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(26) Publication Language: English

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(72) Inventors; and

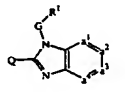
(75) Inventors/Applicants *(for US only)*: JANSSENS, Frans, Eduard [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). LACRAMPE, Jean, Fernand, Armand [FR/FR]; Janssen-Cilag S.A., 1, rue Camille Desmoulins, TSA 91003, F-92787 Issy-les-Moulineaux Cedex 9 (FR). GUILLEMONT, Jérôme, Emile, Georges [FR/FR]; Janssen-Cilag S.A., 1, rue Camille Desmoulins, TSA 91003, F-92787 Issy-les-Moulineaux Cedex 9 (FR). VENET, Marc, Gaston [FR/FR]; Janssen-Cilag S.A., 1, rue Camille Desmoulins, TSA 91003, F-92787 Issy-les-Moulineaux Cedex 9 (FR). ANDRIES, Koenraad, Jozef, Lodenwijk, Marcel [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

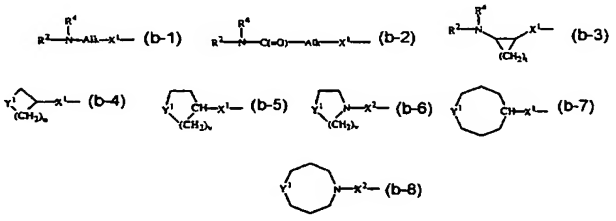
(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Department - 3547, Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS


(I)


(b-1) (b-2) (b-3) (b-4) (b-5) (b-6) (b-7) (b-8)

(57) Abstract: The present invention concerns compounds of formula (I), prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof wherein -a^1=a^2-a^3=a^4- represents a radical of formula -CH=CH-CH=CH-; -N=CH-CH=CH-; -CH=N-CH=CH-; -CH=CH-N=CH-; -CH=CH-CH=N-; wherein each hydrogen atom may optionally be substituted; Q is a radical of formulae (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8), wherein Alk is C_{1-6}alkanediyl; Y^1 is a bivalent radical of formula -NR^2- or -$CH(NR^2R^4)$-; X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $CH(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2; X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl, t is 2 to 5; u is 1 to 5; v is 2 or 3; and whereby each hydrogen in Alk and in (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8), may optionally be replaced by R^3; provided that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 cannot replace a hydrogen atom in the α position relative to a nitrogen atom; G is a direct bond or optionally substituted C_{1-10}alkanediyl; R^1 is an optionally substituted bicyclic heterocycle; R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with another substituent; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy, R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl; R^{5a}, R^{5b}, R^{5c} and R^{5d} are hydrogen or C_{1-6}alkyl; or R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together from a bivalent radical of formula -$(CH_2)_s$- wherein S is 4 or 5; R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl; aryl is optionally substituted phenyl; Het is pyridyl, pyrimidinyl, pyryzinyl, pyridazinyl; as respiratory syncytial virus replication inhibitors; their preparation, compositions containing them and their use as a medicine.

WO 01/00615 A1

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
JAB 1500-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 05677	20/06/2000	28/06/1999
Applicant		
JANSSEN PHARMACEUTICA N.V.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 to 15. relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I where Q is a 1-R2-piperidyl-4-amino or amino(cyclo)alkylamino group and their intermediates as described in the examples of tables 3 to 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
EP 00/05677

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/14 A61K31/4709 A61K31/4375 A61K31/437 A61K31/498
A61K31/4409 A61K31/436 A61P11/00 A61P31/12 C07D471/04
C07D417/14 C07D413/14 C07D409/14 C07D401/06 C07D491/056

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 01697 A (JANSSEN PHARMACEUTICA NV) 6 February 1992 (1992-02-06) page 21, line 9 - line 12; claim 1	1,7
P,X	WO 99 44596 A (JANSSEN PHARMACEUTICA) 10 September 1999 (1999-09-10) page 11, line 18 - line 19; claim 1	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	27/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
EP 00/05677

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 //(C07D471/04,221:00,221:00),(C07D471/04,235:00,221:00),
(C07D491/056,319:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
EP 00/05677

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9201697 A	06-02-1992	AT 188477 T	15-01-2000
		AU 646280 B	17-02-1994
		AU 8209391 A	18-02-1992
		CA 2086546 A	20-01-1992
		CN 1058216 A,B	29-01-1992
		CS 9102239 A	19-02-1992
		DE 69131895 D	10-02-2000
		DE 69131895 T	20-07-2000
		EP 0539420 A	05-05-1993
		ES 2142802 T	01-05-2000
		FI 930199 A	18-01-1993
		GR 3032999 T	31-07-2000
		HU 64066 A	29-11-1993
		IL 98865 A	27-11-1995
		KR 206723 B	01-07-1999
		MX 9100307 A	28-02-1992
		NO 304791 B	15-02-1999
		NZ 238863 A	26-03-1993
		PL 170580 B	31-01-1997
		PT 98366 A,B	29-05-1992
		RU 2067978 C	20-10-1996
		US 5360807 A	01-11-1994
		ZA 9105654 A	31-03-1993
WO 9944596 A	10-09-1999	AU 3408999 A	20-09-1999

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

QUAGHEBEUR, Luc
JANSSEN PHARMACEUTICA N.V.
Patent Department
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	09.07.2001
Applicant's or agent's file reference JAB 1500-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05677	20/06/2000	28/06/1999

Applicant
JANSSEN PHARMACEUTICA N.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 1500-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05677	20/06/2000	28/06/1999

International Patent Classification (IPC) or national classification and IPC
C07D401/14

Applicant
JANSSEN PHARMACEUTICA N.V.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/11/2000	09.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wörth, C Telephone No. +49 89 2399 8726

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05677

I. Basis of the rep rt

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-83 as originally filed

Claims, No.:

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-15 partially.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-15 partially.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. **Reference is made to th following docum nts; they have all been cit d in th written opinion:**

D1: WO 92 01697 A; 6 February 1992 (1992-02-06)
D2: WO 99 44596 A; 10 September 1999 (1999-09-10)
D3: EP 0005318 A (cited by the Applicant)
D4: EP 0297661 A (cited by the Applicant)
D5: EP 0307014 A (cited by the Applicant)
D6: WO 9831363 A
D7: EP 0747363 A
D8: WO 9855120 A
D9: WO 9810764 A
D10 R.R. TIDWELL ET AL: 'Aromatic amidines: comparison of their ability to block respiratory syncytial virus induced cell fusion and to inhibit plasmin, urokinase, thrombin and trypsin', JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 2, pages 294 to 298
D11 CHIBA ET AL.: 'Inhibitory effect of pyridobenzazoles on virus replication in vitro', BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 18, no. 2, pages 1081 to 1083

2. **Non-establishment of opinion with regard to novelty, inventive st p and industrial applicability** (Reference to section III)

The Applicant's attention is drawn to the fact that claims or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (cf. Rule 66.1(e) PCT).
With respect to the international search report dated 13 October 2000, the international preliminary examination of the present application has been carried out for those parts relating to the compounds of formula (I) where radical Q is a 1-R2-piperidyl-4-amino- or amino(cyclo)alkylamino-group as described in the examples of tables 3 to 13.

3. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement (Reference to section V)

3.1 Novelty

Documents D1 and D3-D5 disclose bicyclic heterocycles as anti-allergic compounds, whereas documents D6-D8 disclose benzimidazoles as anti-viral compounds. The novelty rendering feature of the present application with respect to the subject-matter of documents D1 and D3-D8 is the definition of substituent R^1 as a bicyclic heterocycle.

Document D9 discloses a piperazine-derivative, known as anti-allergic compound, as useful for treating anti-viral diseases. The novelty rendering feature of the present application in view of this document is the fused heterocyclic core-molecule.

Documents D10 and D11 disclose fused heterocyclic core-molecules as anti-viral compounds. The novelty rendering feature of the present application with respect to the subject-matter of these documents is inter alia the definition of radical Q.

Accordingly, the present application meets the requirements set forth in Articl 33(2) PCT.

3.2 Inventive step

Documents D6-D8 are considered as to represent the respective closest prior art for some of the claimed families of compounds. These documents disclose N1-C2-substituted benzimidazoles or pyridoimidazoles as anti-viral agents (**see D6**, abstract and page 2, lines 14-22; **see D8**, abstract and page 2, last paragraph; **see D7** page 2, lines 24ff).

In view of these documents, the problem to be solved can be regarded as the provision of further fused 5,6-membered heterocyclic compounds with unexpected effects.

The Applicant's attention is drawn to the point, that in contrast to the description, which alleges anti-viral activities for the subject-matter of the present application, the claimed activity (see claim 7-9 and 15) is at present considered to be "therapeutically effective".

The solution to this problem provided by the present application consists in the analogisation of the N1- and C2-substituents of fused heterocyclic core-molecules or their bioisosteric analogues known from documents D6-D8.

However, the combined technical teaching of documents D1 and D3-D5 clearly indicates a fused heterocycle, substituted at least at positions N1 and C2 of the imidazole-moiety, as therapeutically active lead compound. As a consequence thereof, the man skilled in the art having knowledge of this technical teaching would not be surprised to obtain therapeutically active compounds by broadening the group of possible substituents represented by radical Q or R^1 according to the present application.
Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that for structural similar compounds a similar biological activity can be expected. As a consequence thereof, SAR allow to predict that for formal analogisations a pharmaceutical activity will be maintained.
Therefore, the feature of broadening the group of possible substituents represented by radical Q or R^1 starting from documents D6-D8 is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without any exercise of inventive skill, in order to solve the problem defined above.

As far as the alleged anti-viral activity mentioned in the description of the present application is concerned, attention is drawn to documents D10 and D11.
For the man skilled in the art, having knowledge of the combined technical teaching of

- document D10 (benzimidazoles as anti-viral lead compounds, see page 295, first column, last paragraph),
- document D11 (fused benzimidazoles as compounds exhibiting an inhibitory effect on RSV virus replication; see compounds 1-4, table 1, page 1082),

the feature of the provision of substituted benzimidazoles and their isosteric analogues is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
Furthermore, the inhibiting effect of the well known histamine H1 receptor antagonist cetirizine on viral replication together with an inhibiting effect of RSV-induced cell

modifications disclosed in document D9, page 2, lines 17-22 and page 3, lines 10-13, is a strong indication for a man skilled in the art having knowledge of the technical teaching of documents D7 and D8 (benzimidazole as lead compound for anti-viral agents) to examine, if known anti-allergic compounds bearing a benzimidazole-core exhibit also anti-viral properties, thereby arriving to the solution proposed by the present application.

It is noted, that SAR does not allow to predict whether the activity is better or worse. As a consequence thereof, an **unexpected effect** can be considered as an indication for inventive step. However, the applicant has not shown that the claimed compounds are likely to have any unexpected effects compared to those in the cited documents, in particular the nearest possible compounds.

As far as the scope of the claims is concerned, attention is drawn to the point, that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations like e.g. the definition of radical G are in contradiction to the basis of even **qualitative** structure-activity- relationships. Taking into account the relevant state of the art and the common knowledge, it appears to be not predictable, that all alternatives would achieve the technical effect.

Accordingly, the present application does not fulfill the requirements set forth in Article 33(3) PCT.

4. **Certain documents cited** (Reference to section VI)

The following document disclosing glycine transport inhibitors, which structures appear to overlap with the subject-matter of the present application, may become relevant when entering the national/regional phase.

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99/44596	10 September 1999	26 February 1999	6 March 1998

5. Certain observations in th international application (Reference to section VIIi)

5.1 The terms "prodrug" and "metal complex" in claim 1 and 8 does not fulfill the requirements of Article 6 PCT. The mere term "prodrug" is a functional expression attempting to define the subject-matter in terms of a desired property instead of indicating precisely the technical measures specifically designed to solve the problem. Functional terms will only be allowable if the solution is one which can directly be verified by tests or procedures adequately specified of known to the person skilled in the art and which verification does not need undue experimentation (cf. Guidelines C-III, 4.7). This requirement is presently not fulfilled.

5.2 Contrary to the requirements of Rule 5.1(a)(ii) PCT, documents D6-11 are not identified nor is the relevant background art disclosed therein mentioned.

5.3 Attention is drawn to the fact that dependent claims are only admissible in the case of a allowable independent claim (cf. Rule 6.4 PCT).

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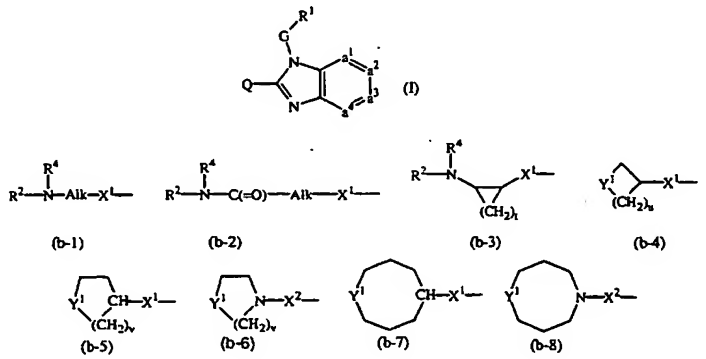
[Continued on next page]

(54) Title: RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS



(57) Abstract: The present invention concerns compounds of formula (I), prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof wherein $-a^1=a^2-a^3=a^4-$ represents a radical of formula -CH=CH-CH=CH-; -N=CH-CH=CH-; -CH=N-CH=CH-; -CH=CH-N=CH-; -CH=CH-CH=N-; wherein each hydrogen atom may optionally be substituted; Q is a radical of formulae (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8), wherein Alk is C_{1-6}alkanediyl; Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$; X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $CH(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2; X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl, t is 2 to 5; u is 1 to 5; v is 2 or 3; and whereby each hydrogen in Alk and in (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8), may optionally be replaced by R^3; provided that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 cannot replace a hydrogen atom in the α position relative to a nitrogen atom; G is a direct bond or optionally substituted C_{1-10}alkanediyl; R^1 is an optionally substituted bicyclic heterocycle; R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with another substituent; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy, R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl; R^{5a}, R^{5b}, R^{5c} and R^{5d} are hydrogen or C_{1-6}alkyl; or R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together from a bivalent radical of formula $-(CH_2)_s-$ wherein S is 4 or 5; R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl; aryl is optionally substituted phenyl; Het is pyridyl, pyrimidinyl, pyryzinyl, pyridazinyl; as respiratory syncytial virus replication inhibitors: their preparation, compositions containing them and their use as a medicine.

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RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

The present invention is concerned with benzimidazoles and imidazopyridines having antiviral activity, in particular, they have an inhibitory activity on the replication of the respiratory syncytial virus. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

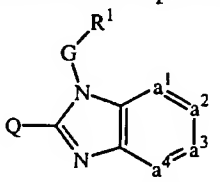
Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. Ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam® and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

EP-A-0,005,318 , EP-A-0,099,139 , EP-A-0,145,037 , EP-A-0,144,101 , EP-A-0,151,826 , EP-A-0,151,824 , EP-A-0,232,937 , EP-A-0,295,742 , EP 0,297,661 , EP-A-0,307,014 , WO 92 01697 describe benzimidazole and imidazopyridine substituted piperidine and piperazine derivatives as antihistaminics, antiallergics or serotonine antagonists.

Thus, the present invention concerns the compounds of formula (I)



(I)

their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

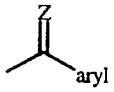
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

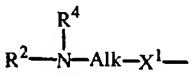
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

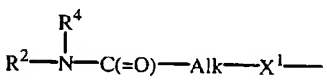


wherein =Z is =O, $=CH-C(=O)-NR^{5a}R^{5b}$, $=CH_2$, $=CH-C_{1-6}$alkyl, =N-OH or $=N-O-C_{1-6}$alkyl;

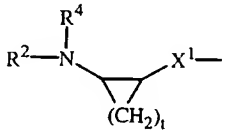
Q is a radical of formula



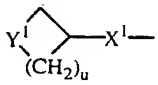
(b-1)



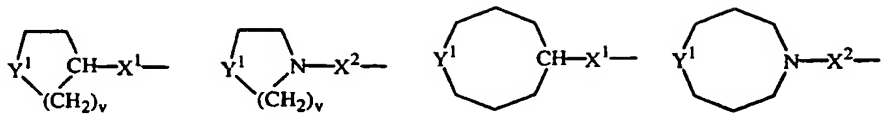
(b-2)



(b-3)



(b-4)



(b-5) (b-6) (b-7) (b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

t is 2, 3, 4 or 5;

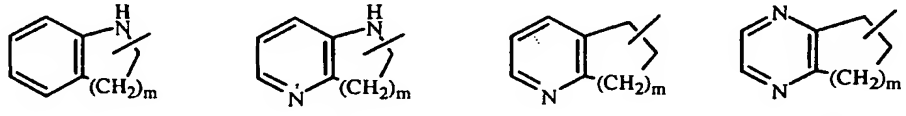
u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

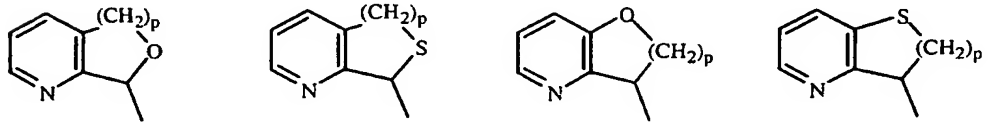
whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one, two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, arylcarbonyl, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, amino, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino and aryl;

R^1 is a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl or a radical of formula



(c-1) (c-2) (c-3) (c-4)



(c-5) (c-6) (c-7) (c-8)

and said bicyclic heterocycles may optionally be substituted in either of the two cycles with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxy-C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)-amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;

each R^2 independently is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5;

R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated.

As used herein C_{1-3}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as methyl, ethyl,

propyl, 1-methylethyl and the like; C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C_{1-3}alkyl and butyl and the like; C_{2-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like; C_{1-9}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 9 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-9}alkyl and decyl, 2-methylnonyl and the like. C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C_{2-5}alkanediyl is substituted on C_{1-10}alkyl as provided for in the definition of R^2, it is meant to be substituted on one carbon atom thus forming a spiro moiety; C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; C_{1-10}alkanediyl is meant to include C_{1-6}alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term (=N-OH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are

attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, they may be the same or different.

As described hereinabove, R^1 defines a bicyclic heterocycle which may optionally be substituted. The substituents may be divided over both rings or they may be attached to one and the same ring.

When any variable (e.g. aryl, R^2,R^3, R^4, R^{5a}, R^{5b} etc.) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I) and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their prodrugs, *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their prodrugs, *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention. As used hereinafter the terms trans or cis are well-known by the person skilled in the art.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically

acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

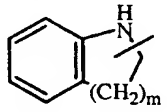
The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complexating properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

A special group of com pounds are those compounds of formula (I) wherein one or more of the following restrictions apply:

- Q is a radical of formula (b-1), (b-3), (b-4), (b-5), (b-6), (b-7) or (b-8);
- X^2 is a direct bond, CH_2 or C(=O);
- R^1 is a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl, or a radical of formula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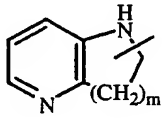
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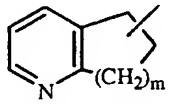
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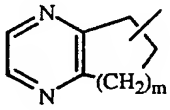
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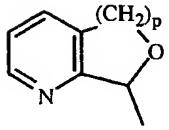
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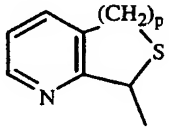
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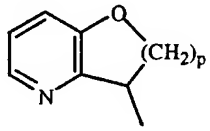
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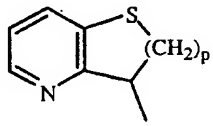

(c-8)

and said bicyclic heterocycles may optionally be substituted in either of the two cycles with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxy-C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)-amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;

- each R^2 independently is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy,

C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;
- R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;
- R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl.

Another special group of compounds are those compounds wherein $-a^1=a^2-a^3=a^4-$ is a radical of formula (a-1), (a-2) or (a-3).

Yet another special group of compounds are those compounds wherein Q is a radical of formula (b-5) wherein v is 2, and Y^1 is $-NR^2-$.

Also interesting compounds are those compounds wherein R^2 is C_{1-10}alkyl substituted with NHR^6.

Other interesting compounds are those compounds wherein G is a direct bond or C_{1-10}alkanediyl optionally substituted with one two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$.

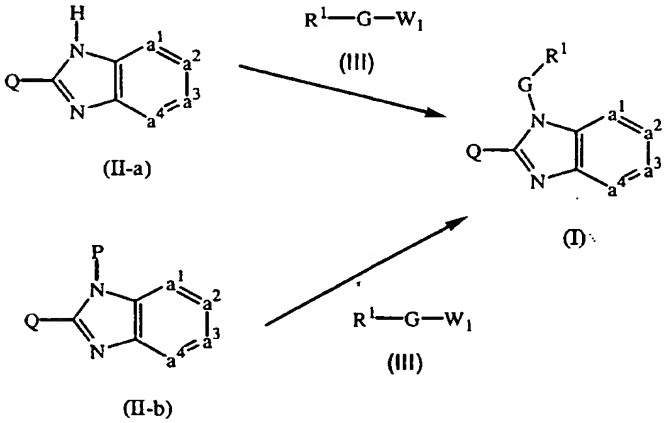
Preferred compounds are :
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-4-methyl-1-[1-(8-quinolinyl)ethyl]-*1H*-benzimidazol-2-amine monohydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-bromo-5,6,7,8-tetrahydro-8-quinolinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-4-methyl-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(1-methyl-*1H*-benzimidazol-4-yl)methyl]-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(ethoxy-8-quinolinylmethyl)-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-7-methyl-3-(8-quinolinylmethyl)-3*H*-imidazo-[4,5-b]pyridin-2-amine tetrahydrochloride trihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-7-methyl-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine tetrahydrochloride monohydrate;

(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(8-quinolinylmethyl)-*1H*-imidazo[4,5-c]pyridin-2-amine trihydrochloride dihydrate;
N-[1-(2-aminoethyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-amine;
N-[1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-yl]-1,3-propanediamine trihydrochloride monohydrate;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-*1H*-benzimidazol-2-amine trihydrochloride dihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(8-quinolinylmethyl)-*1H*-imidazo-[4,5-b]pyridine-2-amine trihydrochloride dihydrate;
(±)-*N*-[1-[1-(aminomethyl)-2-methylpropyl]-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-3-(2-quinolinylmethyl)-3*H*-imidazo-[4,5-b]pyridin-2-amine trihydrochloride trihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(1-isoquinolinylmethyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-(5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
the prodrugs, the *N*-oxides, the addition salts, the quaternary amines, the metal complexes and the stereochemically isomeric forms thereof.

Most preferred compounds are :
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-(quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine trihydrochloride.trihydrate;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(5,6,7,8-tetrahydro-2,3-dimethyl-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinyl-methyl]-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl-1-(3-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(3-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine trihydrochloride dihydrate;

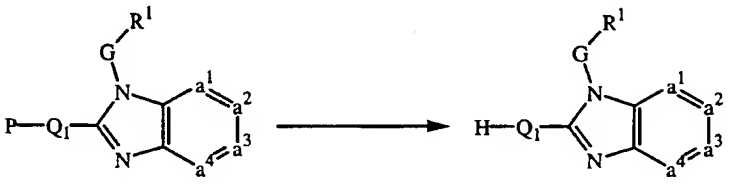
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-4-methyl-*1H*-benzimidazol-2-amine monohydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-(8-quinolinylmethyl)-3*H*-imidazo-[4,5-c]pyridin-2-amine trihydrochloride tetrahydrate;
(±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]-pyridin-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(1-methyl-*1H*-benzimidazol-4-yl)methyl]-*1H*-benzimidazol-2-amine;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine;
the prodrugs, the *N*-oxides, the addition salts, the quaternary amines, the metal complexes and the stereochemically isomeric forms thereof.

In general, compounds of formula (I) can be prepared by reacting an intermediate of formula (II-a) or (II-b), wherein P represents a protecting group, such as, for example C_{1-4}alkyloxycarbonyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991), with an intermediate of formula (III), wherein W_1 is a suitable leaving group, such as a halo atom, e.g. chloro, bromo, in the presence of a suitable base, such as, e.g. sodium hydride. Said reaction can be performed in a reaction-inert solvent, such as *N*,*N*-dimethylformamide.



Compounds of formula (I) wherein, in the definition of Q, R^2 or at least one R^6 substituent is hydrogen, said Q being represented by H-Q_1, and said compounds being represented by formula (I-a), can be prepared by deprotecting an intermediate of formula (IV) wherein P represents a protecting group, for example C_{1-4}alkyloxycarbonyl, benzyl, or those protecting groups mentioned in Chapter 7 of

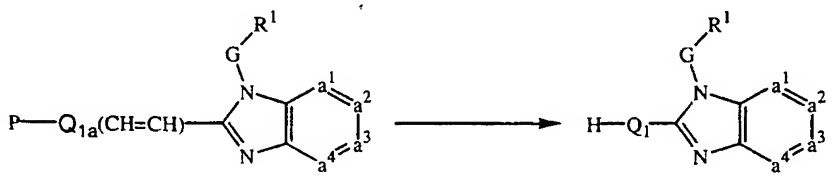
'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991).



(IV) (I-a)

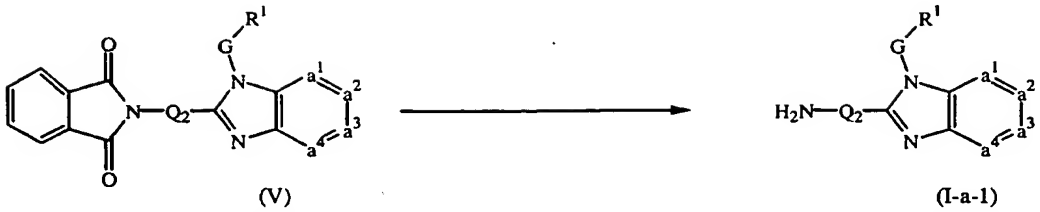
When P represents, for example, C_{1-4}alkyloxycarbonyl, said deprotection reaction can be performed by, for example, acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol and the like. In order to enhance the rate of the reaction, it is advantageous to heat the reaction mixture, in particular up to the reflux temperature. Alternatively, when P represents, for example, benzyl, the deprotection reaction can be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

The catalytic hydrogenation reaction described above can also be used to prepare a compound of formula (I-a) by deprotecting and reducing an intermediate of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(CH=CH)$, and said intermediate being represented by formula (IV-a).



(IV-a) (I-a)

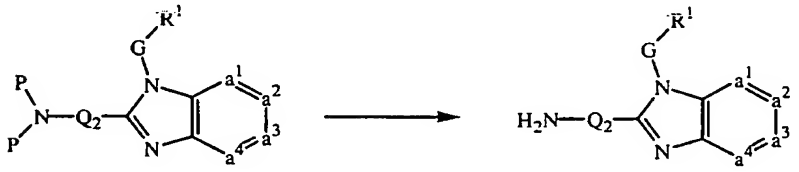
Compounds of formula (I) wherein, in the definition of Q, both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, said Q being represented by H_2N-Q_2, and said compounds being represented by formula (I-a-1), can also be prepared by deprotecting an intermediate of formula (V).



(V) (I-a-1)

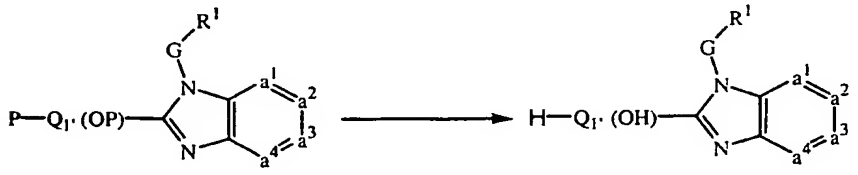
Said deprotection reaction can be performed in the presence of a suitable base such as, for example hydrazine, or in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, such as an alcohol, acetic acid and the like.

Compounds of formula (I-a-1) can also be prepared by deprotecting an intermediate of formula (VI) according to the procedure described for the preparation of compounds of formula (I-a).

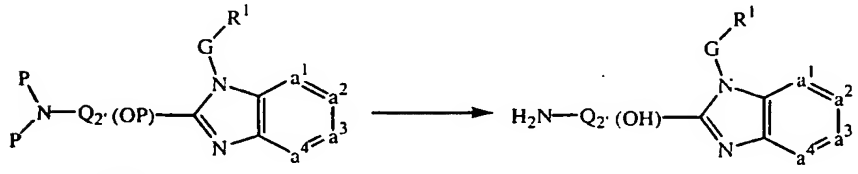


(VI) (I-a-1)

Compounds of formula (I-a) or (I-a-1), wherein Q_1 or Q_2 comprise a hydroxy substituent, said Q_1 or Q_2 being represented by Q_1-(OH) or Q_2-(OH), and said compounds being represented by formula (I-a-2) or (I-a-1-1), can be prepared by deprotecting an intermediate of formula (VII) or (VIII) as described hereinabove for the preparation of compounds of formula (I-a).

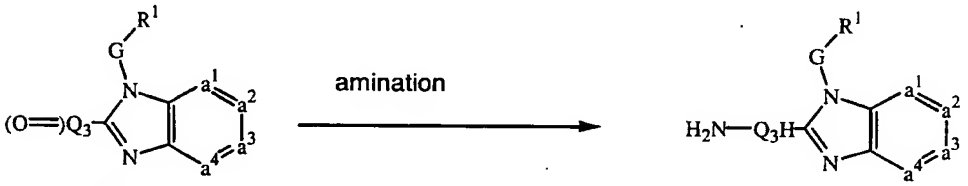


(VII) (I-a-2)



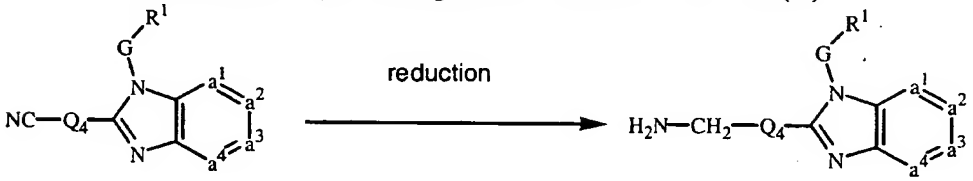
(VIII) (I-a-1-1)

Compounds of formula (I) wherein, in the definition of Q, both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, said Q being represented by H_2N-Q_3H, and said compounds being represented by formula (I-a-1-2) can also be obtained by reductive amination of intermediates of formula (IX) in the presence of a suitable amination reagent, such as, for example, ammonia, hydroxylamine, or benzylamine, and in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst. An appropriate catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, rhodium-on-Al_2O_3, and the like, optionally in the presence of a catalyst poison, such as a thiophene solution. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



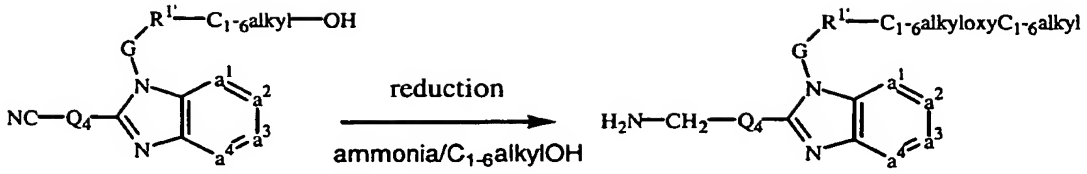
(IX) (I-a-1-2)

Compounds of formula (I), wherein Q comprises a $-CH_2NH_2$ moiety, said Q being represented by H_2N-CH_2-Q_4, and said compounds being represented by formula (I-a-1-3) can be prepared by reducing an intermediate of formula (X).



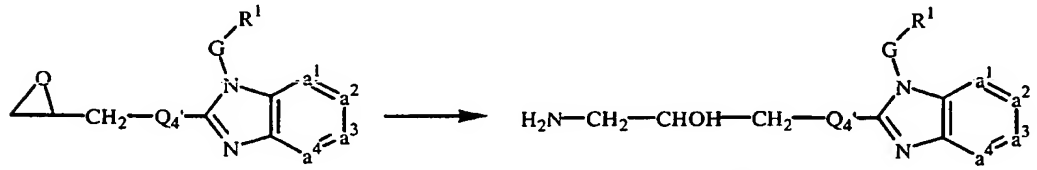
(X) (I-a-1-3)

Said reduction can be performed with a suitable reducing agent, such as lithium aluminium hydride or hydrogen, optionally in the presence of a suitable catalyst, such as Raney Nickel. A suitable solvent for the above reaction is, for example, tetrahydrofuran, or a solution of ammonia in an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like. Said reduction reaction performed in a solution of ammonia in an alcohol can also be used to prepare compounds of formula (I-a-1-3), wherein R^1 is substituted with C_{1-6}alkyloxyC_{1-6}alkyl, said R^1 being represented by $R^{1''}$-C_{1-6}alkyloxyC_{1-6}alkyl, and said compounds being represented by formula (I-a-1-3-1) starting from an intermediate of formula (X-a).



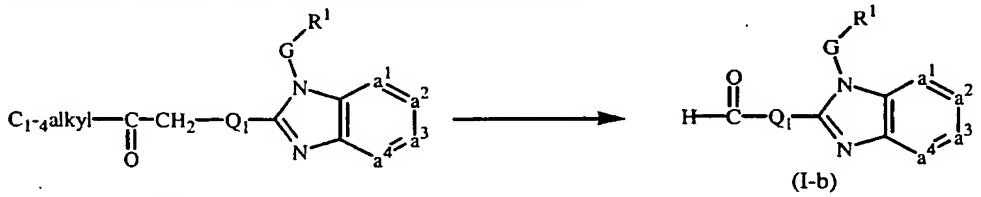
(X-a) (I-a-1-3-1)

Compounds of formula (I), wherein Q comprises a -CH_2-CHOH-CH_2-NH_2 moiety, said Q being represented by H_2N-CH_2-CHOH-CH_2-Q_4', and said compounds being represented by formula (I-a-1-3-2), can be prepared by reacting an intermediate of formula (XI) with ammonia in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol.



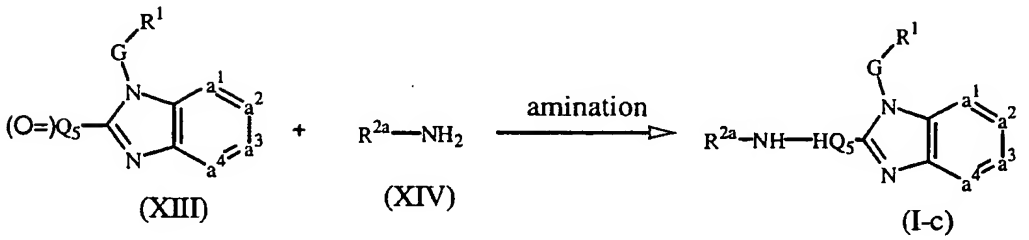
(XI) (I-a-1-3-2)

Compounds of formula (I), wherein, in the definition of Q, R^2 or one R^6 substituent is formyl, said Q being represented by H-C(=O)-Q_1, and said compounds being represented by formula (I-b), can be prepared by reacting an intermediate of formula (XII) with formic acid, formamide and ammonia.



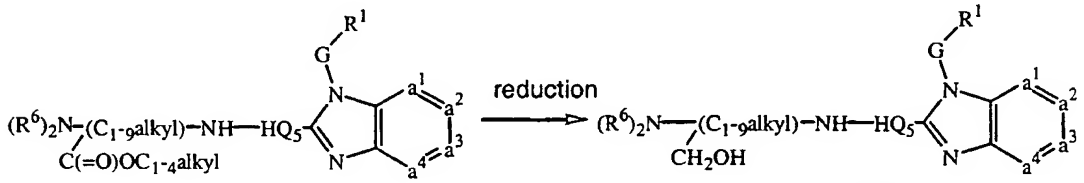
(XII) (I-b)

Compounds of formula (I), wherein, in the definition of Q, R^2 is other than hydrogen, said R^2 being represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, said Q being represented by R^{2a}-NH-HQ_5, and said compounds being represented by formula (I-c), can be prepared by reductive amination of an intermediate of formula (XIII) with an intermediate of formula (XIV) in the presence of a suitable reducing agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



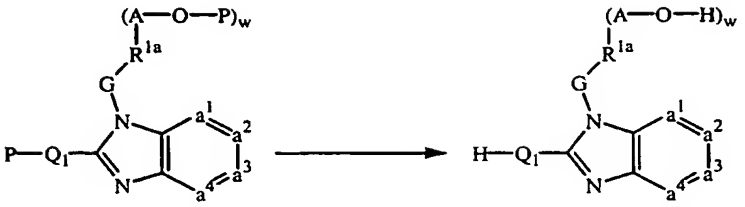
(XIII) (XIV) (I-c)

Compounds of formula (I-c), wherein R^{2a} represents C_{1-10}alkyl substituted with $N(R^6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, said R^{2a} being represented by $[(C_{1-9}alkyl)CH_2OH]$-$N(R^6)_2$, and said compounds being represented by formula (I-c-1), can be prepared by reducing an intermediate of formula (XV) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, such as tetrahydrofuran.

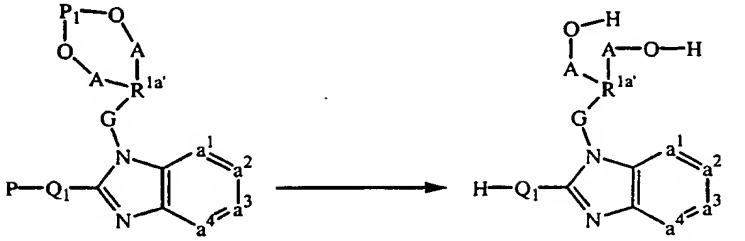


(XV) (I-c-1)

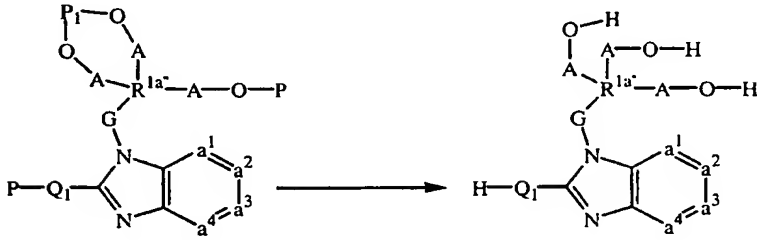
Compounds of formula (I) wherein, in the definition of Q, R^2 or one R^6 substituent is hydrogen, said Q being represented by $H\text{-}Q_1$, and wherein R^1 is a bicyclic heterocycle substituted with 1 or more substituents selected from hydroxy, hydroxyC_{1-6}alkyl, or $HO(\text{-}CH_2\text{-}CH_2\text{-}O)_n$-, said substituents being represented by formula A-OH, said R^1 being represented by R^{1a}-$(A\text{-}OH)_w$, with w being the amount of substituents on R^{1a} ranging from 1 to 4, and said compounds being represented by formula (I-d), can be prepared by deprotecting an intermediate of formula (XVI) with a suitable acid, such as hydrochloric acid and the like, optionally in the presence of a suitable solvent, such as an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like. Alternatively, one protecting group may also protect more than one substituent of R^{1a}, said protecting group being represented by P_1, as represented by formula (XVI-a). The two ways of protecting the substituents of R^{1a}, i.e. with a separate, as in formula (XVI), or a combined, as in formula (XVI-a), protecting group, may also be combined in the same intermediate, as represented by formula (XVI-b).



(XVI) (I-d)

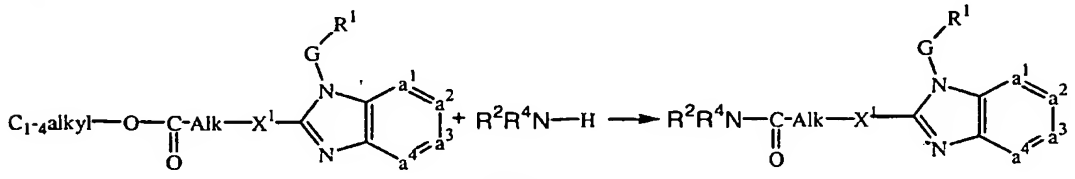


(XVI-a) (I-d-1)



(XVI-b) (I-d-2)

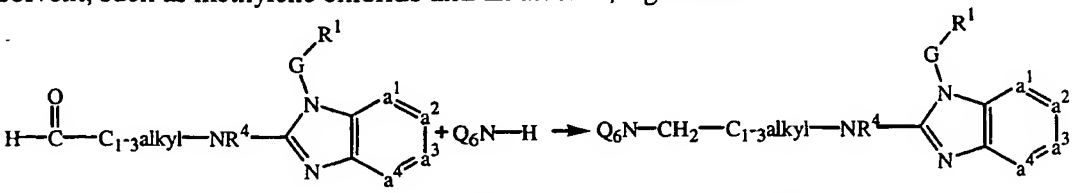
Compounds of formula (I), wherein Q is a radical of formula (b-2), said compounds being represented by formula (I-e), can be prepared by reacting an intermediate of formula (XVII) with an intermediate of formula (XVIII) in the presence of sodium cyanide and a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.



(XVII) (XVIII) (I-e)

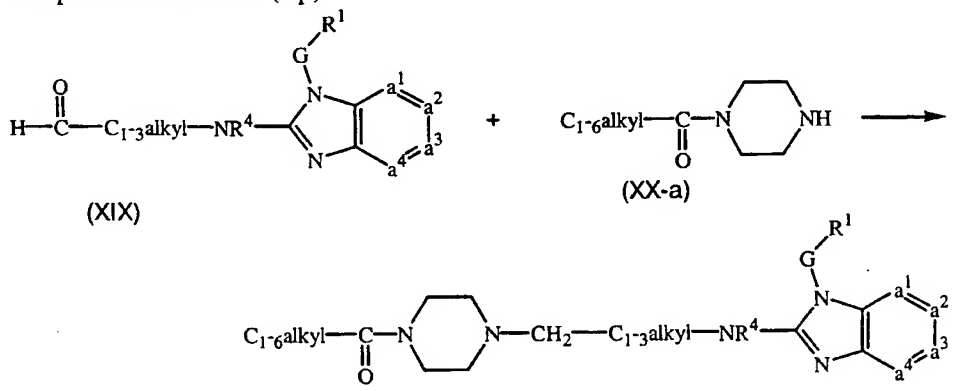
Compounds of formula (I), wherein in the definition of Q, X^2 is C_{2-4}alkyl-NR^4, said Q being represented by Q_6N-CH_2-C_{1-3}alkyl-NR^4, and said compounds being represented by formula (I-p), can be prepared by reacting an intermediate of formula (XIX) with an intermediate of formula (XX) in the presence of isopropyl titanate (IV) and a suitable

reducing agent, such as $NaBH_3CN$, and in the presence of a suitable reaction-inert solvent, such as methylene chloride and an alcohol, e.g. ethanol.



(XIX) (XX) (I-p)

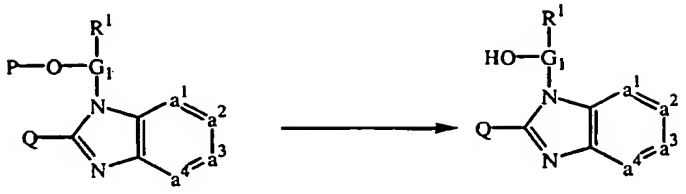
Compounds of formula (I-p), wherein R^2 is C_{1-6}alkylcarbonyl, and Q is a radical of formula (b-6), wherein Y^1 is NR^2, said compounds being represented by formula (I-p-1), can be prepared by reacting an intermediate of formula (XIX) with an intermediate of formula (XX-a) according to the procedure described for the preparation of a compound of formula (I-p).



(XIX) (XX-a)

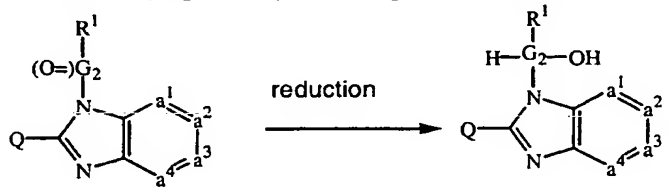
(I-p-1)

Compounds of formula (I), wherein G is substituted with hydroxy or $HO(-CH_2CH_2O)_n-$, said G being represented by G_1-OH, and said compounds being represented by formula (I-q), may be prepared by deprotecting an intermediate of formula (XXI), wherein P represents a suitable protecting group, for example, benzyl. Said deprotection reaction can be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.



(XXI) (I-q)

Compounds of formula (I), wherein G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, said G being represented by H-G_2-OH, and said compounds being represented by formula (I-q-1), can also be prepared by reducing an intermediate of formula (XXII).



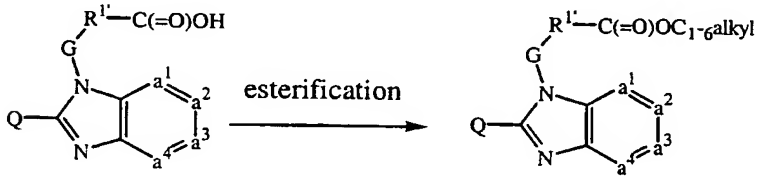
(XXII) (I-q-1)

Said reduction reaction can be performed in the presence of a suitable reducing agent, such as, for example sodium borohydride, in a reaction-inert solvent, such as an alcohol or tetrahydrofuran or a mixture thereof. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter.

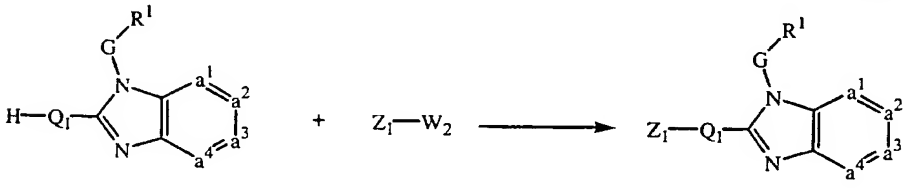
The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise; for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Compounds of formula (I), wherein R^1 is a bicyclic heterocycle substituted with C_{1-6}alkyloxycarbonyl, said R^1 being represented by $R^{1'}$-C(=O)OC_{1-6}alkyl, and said compounds being represented by formula (I-f), can be prepared by esterification of a compound of formula (I-g) in the presence of a suitable alcohol, e.g. methanol, ethanol, propanol, butanol, pentanol, hexanol and the like, and in the presence of a suitable acid, such as hydrochloric acid and the like.



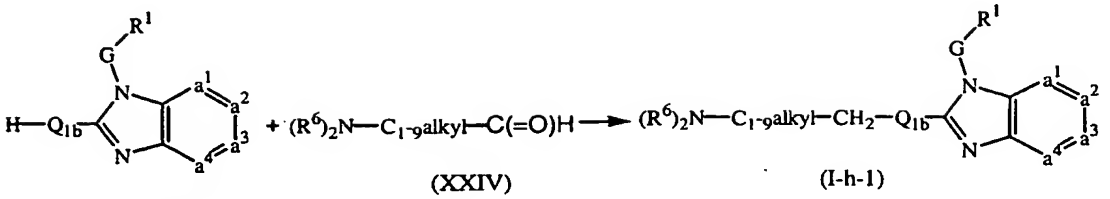
(I-g) (I-f)

Compounds of formula (I-a) may be converted into compounds of formula (I) wherein, in the definition of Q, R^2 or at least one R^6 substituent is other than hydrogen, said R^2 or R^6 being represented by Z_1, said Q being represented by Z_1-Q_1, and said compounds being represented by formula (I-h), by reaction with a reagent of formula (XXIII), wherein W_2 is a suitable leaving group, such as a halo atom, e.g. bromo, or 4-methylbenzenesulphonate, in the presence of a suitable base, such as, for example disodium carbonate, dipotassium carbonate, sodium hydroxide and the like, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, acetonitrile, *N*,*N*-dimethylformamide.



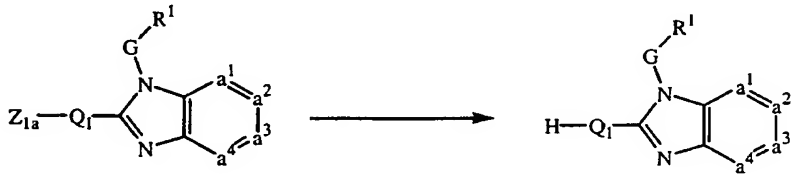
(I-a) (XXIII) (I-h)

Compounds of formula (I-h), wherein, in the definition of Z_1, R^2 is CH_2-C_{1-9}alkyl substituted with $N(R^6)_2$, said compounds being represented by formula (I-h-1), can also be prepared by reacting a compound of formula (I-a) wherein, in the definition of H-Q_1, R^2 is hydrogen, said H-Q_1 being represented by H-Q_{1b}, and said compounds being represented by formula (I-a-3), with an intermediate of formula (XXIV), in the presence of a suitable reducing agent, such as sodium cyanoborohydride, in a suitable reaction-inert solvent, such as an alcohol.



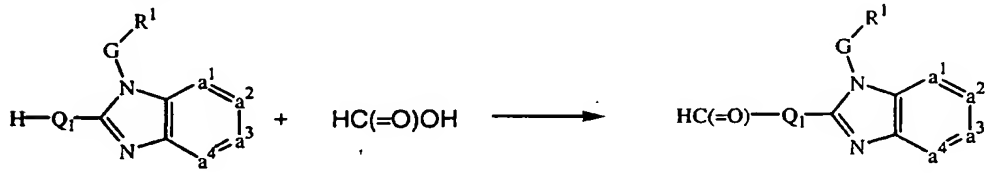
(I-a-3) (XXIV) (I-h-1)

Compounds of formula (I-h), wherein Z_1 comprises formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl or C_{1-6}alkyloxycarbonyl, said Z_1 being represented by Z_{1a}, and said compounds being represented by formula (I-h-2), can be converted into compounds of formula (I-a), by acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol, sec. butanol and the like. In order to enhance the rate of the reaction, it is advantageous to work at elevated temperatures.



(I-h-2) (I-a)

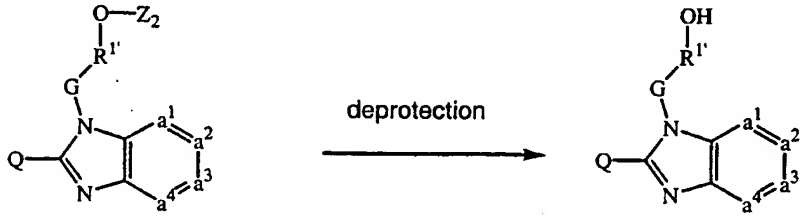
Compounds of formula (I-b) can be prepared by reacting a compound of formula (I-a) with formic acid.



(I-a) (I-b)

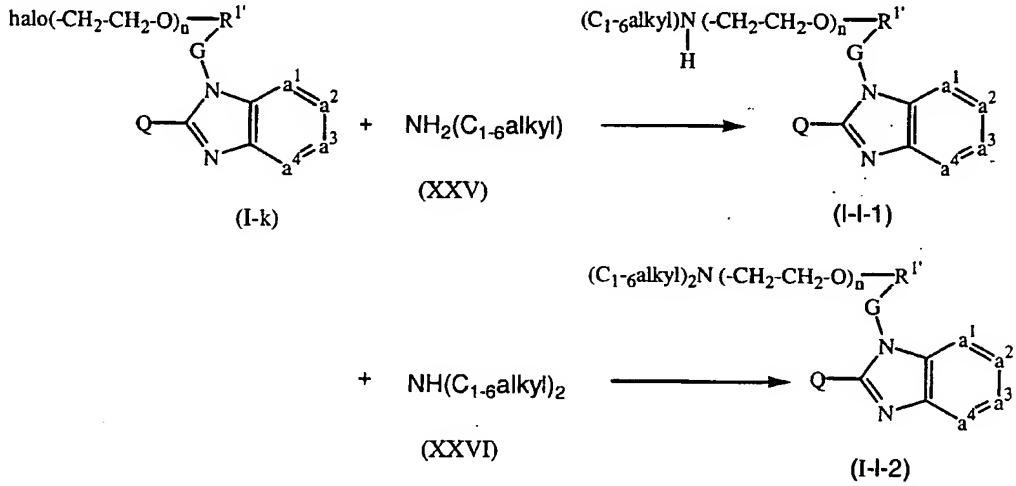
Compounds of formula (I) wherein R^1 is a bicyclic heterocycle substituted with hydroxy, said R^1 being represented by HO-$R^{1'}$, and said compounds being represented by formula (I-i), can be prepared by deprotecting a compound of formula (I-j), wherein R^1 is a bicyclic heterocycle substituted with C_{1-6}alkyloxy or arylC_{1-6}alkyloxy, said C_{1-6}alkyl or arylC_{1-6}alkyl being represented by Z_2, and said R^1 being represented by Z_2-O-$R^{1'}$. Said deprotection can be performed in a reaction-inert solvent, such as, for

example methylene chloride, in the presence of a suitable deprotecting agent, e.g. tribromoborane.



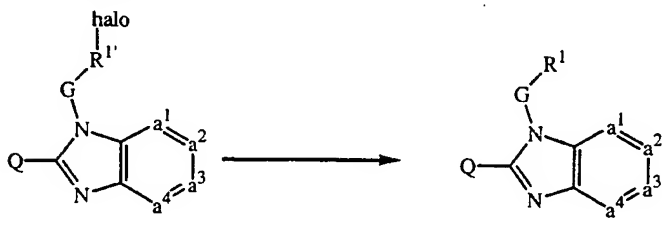
(I-j) (I-i)

Compounds of formula (I) wherein R^1 is a bicyclic heterocycle substituted with halo(-CH_2-CH_2-O)$_n$, said compounds being represented by formula (I-k), can be converted into compounds of formula (I-l-1) or (I-l-2) by reaction with an appropriate amine of formula (XXV) or (XXVI) in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



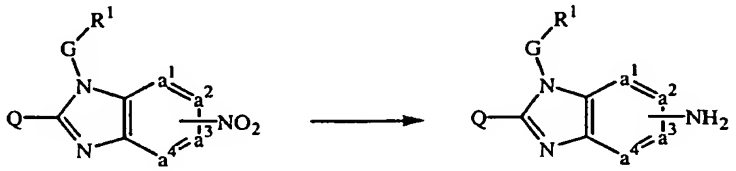
(I-k) (I-l-1) (I-l-2)

Compounds of formula (I) wherein R^1 is a bicyclic heterocycle substituted with halo, said compounds being represented by formula (I-m) can be converted into compounds of formula (I) by reaction with 1-butanethiol in the presence of palladium-on-charcoal and CaO in a suitable reaction-inert solvent, such as tetrahydrofuran.



(I-m) (I)

Compounds of formula (I) wherein a hydrogen atom in the radicals of formula (a-1), (a-2), (a-3), (a-4) or (a-5) is replaced by nitro, said compounds being represented by formula (I-n) may be reduced to a compound of formula (I-o) in the presence of a suitable reducing agent, such as hydrogen, optionally in the presence of a suitable catalyst, such as platinum-on-charcoal, and optionally in the presence of a suitable catalyst poison, e.g. a thiophene solution. The reaction may be performed in a suitable reaction-inert solvent, such as an alcohol.

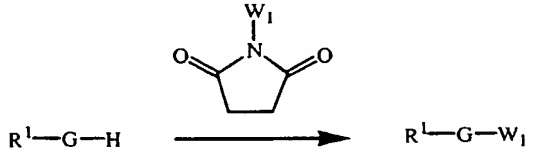


(I-n) (I-o)

In the following paragraphs, there are described several methods of preparing the intermediates in the foregoing preparations. A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to conventional reaction procedures generally known in the art or analogous to the procedures described in EP-A-0005318, EP-A-0099139, EP-A-0151824 , EP-A-0151826 , EP-A-0232937 , EP-A-0295742 , EP-A-0297661 , EP-A-0539420 , EP-A-0539421 , US 4,634,704 , US 4,695,569.

In the foregoing and the following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

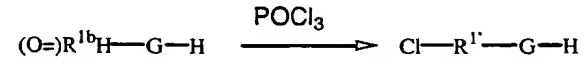
Intermediates of formula (III) can be prepared by reacting an intermediate of formula (XXVII) with a suitable leaving group, i.e. W_1, introducing agent, e.g. 1-halo-2,5-pyrrolidinedione in the presence of dibenzoyl peroxide, in a reaction-inert solvent, e.g. tetrachloromethane.



(XXVII) (III)

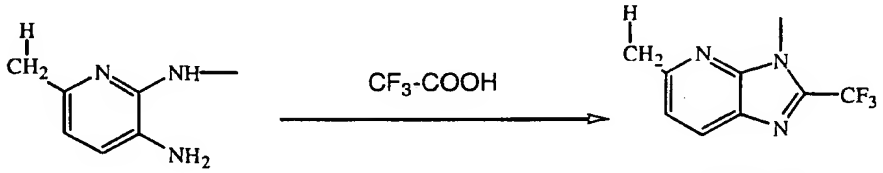
Intermediates of formula (XXVII), wherein R^1 is a bicyclic heterocycle substituted with chloro, said R^1 being represented by Cl-$R^{1'}$ and said intermediates being represented by formula (XXVII-a) can be prepared by reacting an intermediate of formula (XXVIII),

wherein (O=)$R^{1b}H$ is defined as a carbonyl derivative of $R^{1'}$ wherein one carbon or nitrogen, adjacent to the carbonyl, carries at least one hydrogen, with phosphorus oxychloride. Intermediates of formula (XXVIII) may also react as their enol tautomeric forms.



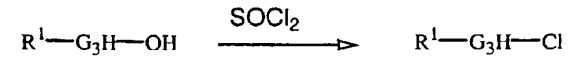
(XXVIII) (XXVII-a)

Intermediates of formula (XXVII), wherein R^1 is 2-trifluoromethyl-3-methyl (3*H*)-imidazo[4,5-b]pyridine, and G is CH_2, said intermediates being represented by formula (XXVII-b), can be prepared by reacting N-2,6-dimethyl-2,3-pyridinediamine (Heterocycles, 38, p 529, 1994), with trifluoroacetic acid.



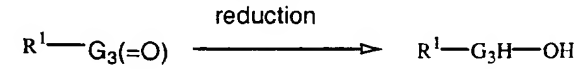
(XXVII-b)

Intermediates of formula (III) wherein W_1 is chloro, which is attached to a carbon atom carrying at least one hydrogen, said G being represented by G_3H, and said intermediates being represented by formula (III-a) can also be prepared by reacting an intermediate of formula (XXIX) with thionylchloride in a reaction-inert solvent, e.g. methylenechloride.



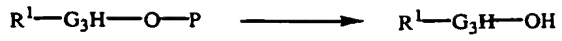
(XXIX) (III-a)

Intermediates of formula (XXIX) can be prepared by reducing an intermediate of formula (XXX) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. sodium borohydride.



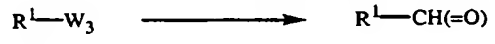
(XXX) (XXIX)

Alternatively, intermediates of formula (XXIX) can also be prepared by deprotecting an intermediate of formula (XXXI), wherein P is a suitable protecting group, e.g. C_{1-4}alkylcarbonyl, in a reaction-inert solvent, such as an alcohol, in the presence of a suitable base, e.g. sodium hydroxide.



(XXXI) (XXIX)

Intermediates of formula (XXX), wherein G_3(=O) is CH(=O), said intermediates being represented by formula (XXX-a), can be prepared by reacting an intermediate of formula (XXXII), wherein W_3 is a suitable leaving group, such as a halo atom, e.g. bromo, with *N,N*-dimethylformamide in the presence of butyllithium in a reaction-inert solvent, e.g. tetrahydrofuran, diethylether or a mixture thereof.

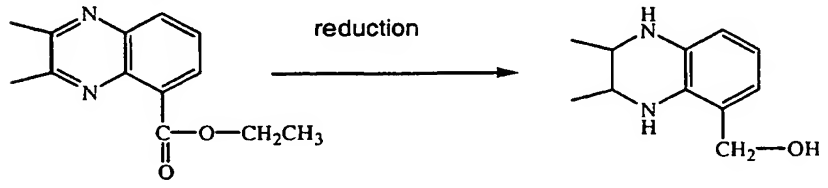


(XXXII) (XXX-a)

Intermediates of formula (XXX-a) can also be prepared by oxidizing an intermediate of formula R^1-CH_2-OH in the presence of a suitable oxidizing agent, e.g. MnO_2 in a reaction-inert solvent, e.g. methylenechloride.

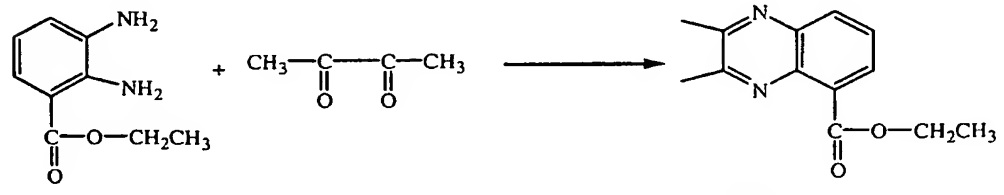
(XXX-a)

Intermediates of formula R^1-CH_2-OH, wherein R^1 is 2,3-dimethylquinoxaline, said intermediates being represented by formula (XCI) can be prepared by reducing an intermediate of formula (XCII) in a reaction-inert solvent, e.g. tetrahydrofuran, in the presence of a suitable reducing agent, e.g. potassium borohydride in the presence of lithium chloride.



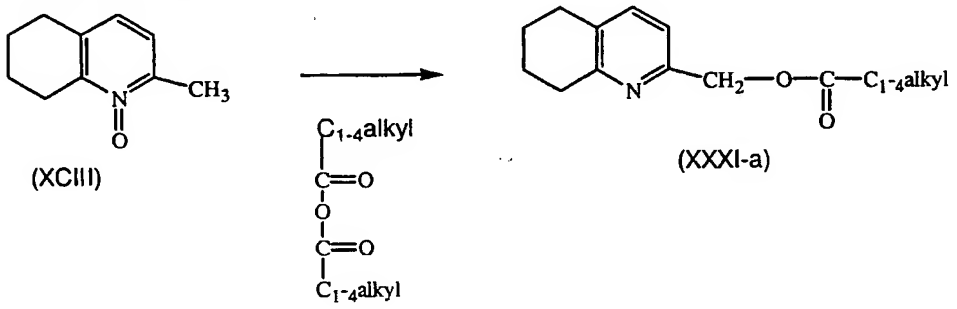
(XCII) (XCI)

Intermediates of formula (XCII) can be prepared by reacting ethyl 2,3-diaminobenzoate (Tetrahydron, 28, 3271, 1972) with 2,3-butanedione in the presence of disodium disulfite.



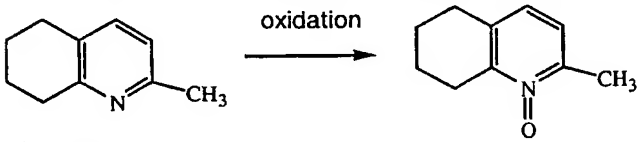
(XCII)

Intermediates of formula (XXXI), wherein R^1 is 5,6,7,8-tetrahydroquinoline, which can optionally be substituted, G_3H is CH_2, and P is C_{1-4}alkylcarbonyl, said intermediates being represented by formula (XXXI-a) can be prepared by reacting an intermediate of formula (XCIII) with C_{1-4}alkylacid anhydride at elevated temperatures in the presence of a suitable base, e.g. sodium hydroxide.



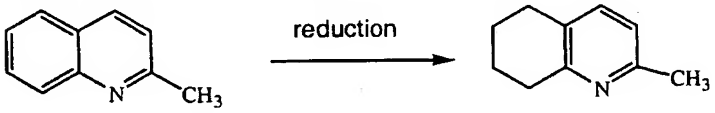
(XCIII) (XXXI-a)

Intermediates of formula (XCIII) can be prepared by oxidizing an intermediate of formula (XCIV) with a suitable oxidizing agent, e.g. a peroxide such as 3-chloro-benzenecarboperoxoic acid, in a reaction-inert solvent, e.g. methylene chloride.



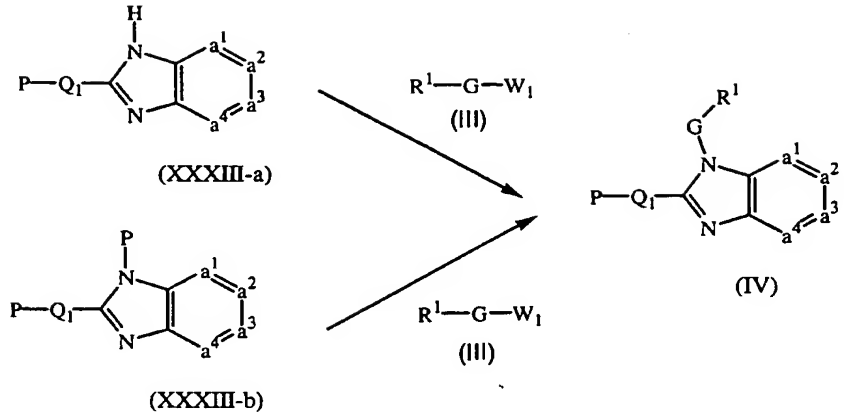
(XCIV) (XCIII)

Intermediates of formula (XCIV) can be prepared by reducing an intermediate of formula (XCV) (Org. Prep. Proced. Int., 23, p 386-387, 1991) with an appropriate reducing agent, e.g. hydrogen, in the presence of a suitable catalyst, e.g. palladium-on-charcoal, and a suitable acid, e.g. trifluoroacetic acid.

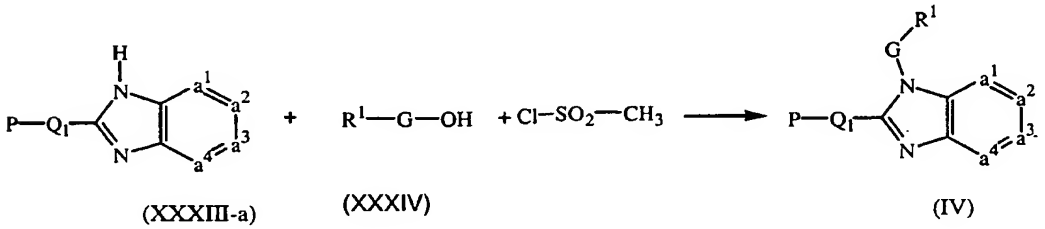


(XCV) (XCIV)

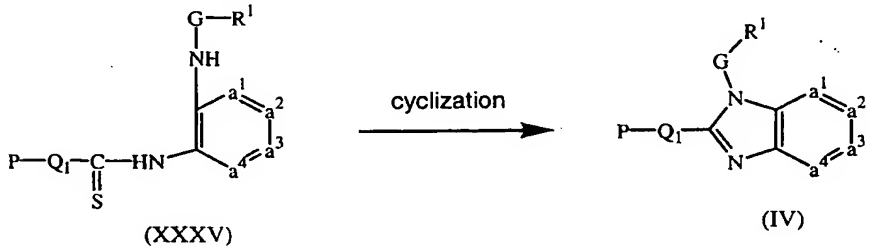
Intermediates of formula (IV) can be prepared by reacting an intermediate of formula (XXXIII-a) or (XXXIII-b), wherein P represents a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, with an intermediate of formula (III) according to the reaction described for the general preparation of compounds of formula (I).



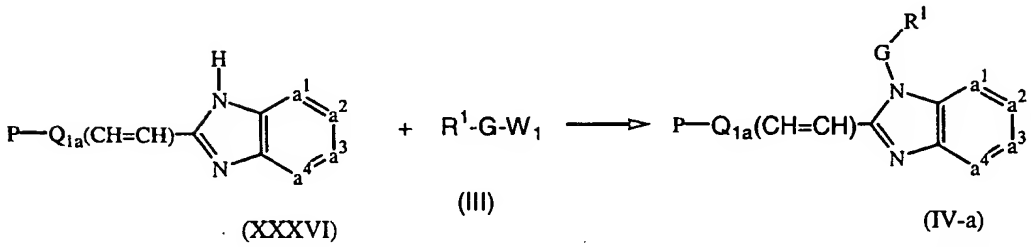
Intermediates of formula (IV) can also be prepared by reacting an intermediate of formula (XXXIII-a) with an intermediate of formula (XXXIV) that has reacted with methanesulfonyl chloride, in the presence of a suitable base, such as sodium hydride, and in the presence of a suitable reaction-inert solvent, e.g. *N*,*N*-dimethylformamide.



Intermediates of formula (IV) can also be prepared by a cyclization reaction of an intermediate of formula (XXXV) in a reaction-inert solvent, e.g. an alcohol or *N*,*N*-dimethylformamide, in the presence of mercury oxide and sulphur.

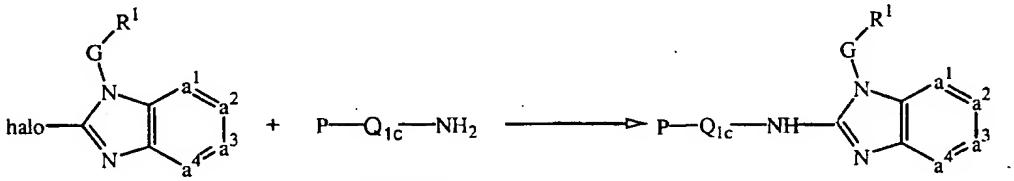


Intermediates of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by Q_{1a}(CH=CH), and said intermediates by formula (IV-a), can be prepared by reacting an intermediate of formula (XXXVI) with an intermediate of formula (III) in the presence of a suitable base, such as dipotassium carbonate.



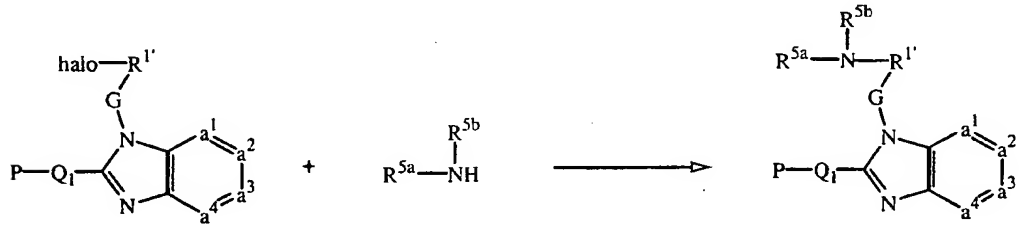
(XXXVI) (III) (IV-a)

Intermediates of formula (IV) wherein, in the definition of Q_1, the X^1 or X^2 moieties in the radicals of formula (b-1) to (b-8) represent NH, said Q_1 being represented by Q_{1c}-NH, and said intermediates by formula (IV-b), may also be prepared by reacting an intermediate of formula (XXXVII) with an intermediate of formula (XXXVIII).



(XXXVII) (XXXVIII) (IV-b)

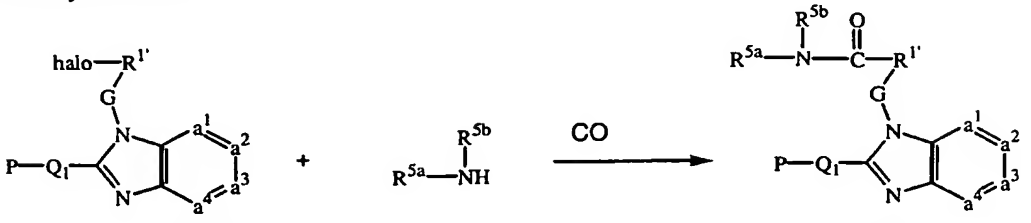
Intermediates of formula (IV) wherein R^1 is a bicyclic heterocycle substituted with amino or mono- or di(C_{1-6}alkyl)amino, said R^1 being represented by $R^{5a}R^{5b}N$-$R^{1'}$, wherein R^{5a} and R^{5b} are defined as described above, and said intermediates being represented by formula (IV-c), can be prepared by reacting an intermediate of formula (XXXIX) with an appropriate amine, represented by formula (XL), in the presence of an appropriate catalyst, e.g. palladium, and (R)-(+)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



(XXXIX) (XL) (IV-c)

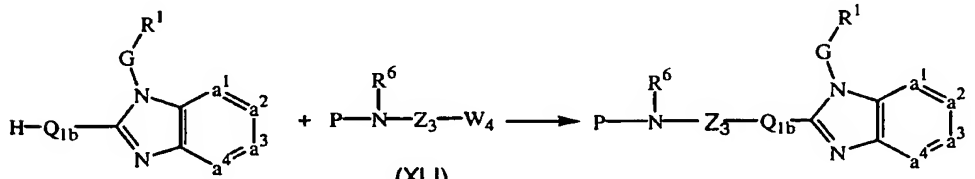
Intermediates of formula (IV) wherein R^1 is a bicyclic heterocycle substituted with C(=O)-$NR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} are defined as described above, said R^1 being represented by $R^{5a}R^{5b}N$-C(=O)-$R^{1'}$, and said intermediates being represented by formula (IV-d), can be prepared by reacting an intermediate of formula (XXXIX) with an appropriate amine, represented by formula (XL), under an atmosphere of carbon monoxide, in the presence of a suitable catalyst, e.g. palladium (II) acetate, and

1,3-bis(diphenylphosphino)propane, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



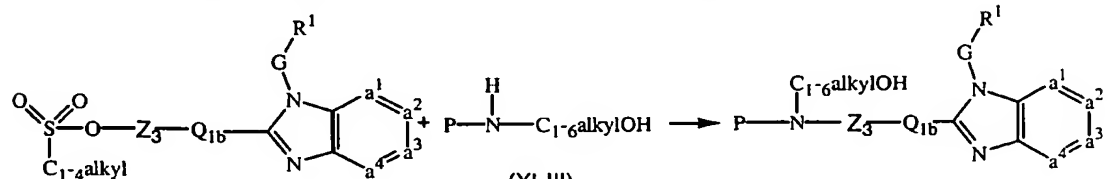
(XXXIX) (XL) (IV-d)

Intermediates of formula (IV) wherein P-Q_1 comprises C_{1-10}alkyl or C_{3-7}cycloalkyl substituted with NR^6-P, said C_{1-10}alkyl or C_{3-7}cycloalkyl being represented by Z_3, said P-Q_1 being represented by P-NR^6-Z_3-Q_{1b}, and said intermediates being represented by formula (IV-e), can be prepared by reacting a compound of formula (I-a-3) with an intermediate of formula (XLI), wherein W_4 represents a suitable leaving group, such as p-toluenesulphonate. Said reaction can be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(I-a-3) (XLI) (IV-e)

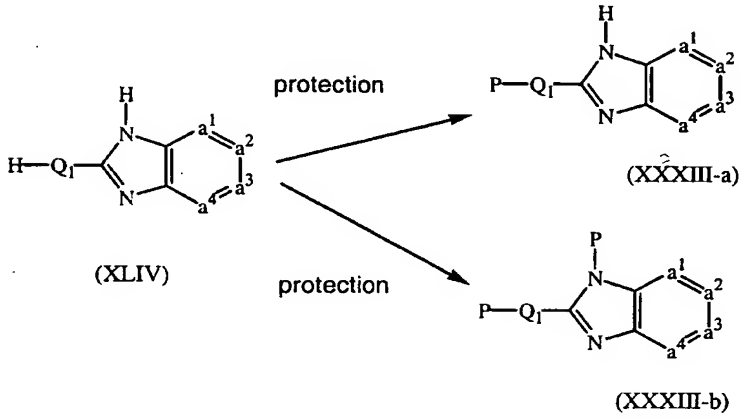
Intermediates of formula (IV-e), wherein R^6 is hydroxyC_{1-6}alkyl, said intermediates being represented by formula (IV-e-1), can be prepared by reacting an intermediate of formula (XLII) with an intermediate of formula (XLIII) in the presence of a suitable base, e.g. dipotassium carbonate, and a suitable solvent, e.g. acetonitrile.



(XLII) (XLIII) (IV-e-1)

Intermediates of formula (XXXIII-a) or (XXXIII-b) can be prepared by protecting an intermediate of formula (XLIV) with a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, in a reaction-inert solvent, such as methylene chloride or an alcohol, e.g. methanol, ethanol, 2-propanol and the like, in the presence of a suitable

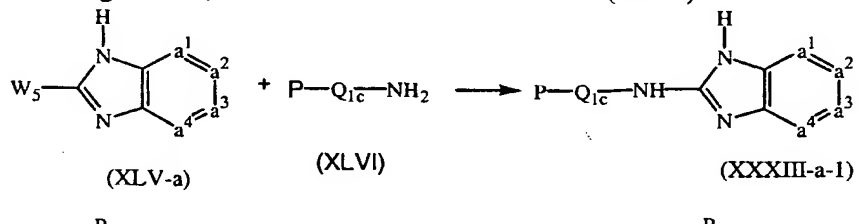
reagent, e.g. di C_{1-4}alkyl dicarbonate and optionally in the presence of a suitable base, e.g. sodium acetate.



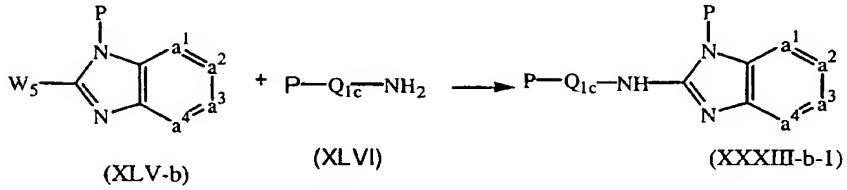
(XLIV) (XXXIII-a) (XXXIII-b)

Alternatively, intermediates of formula (XXXIII-a) or (XXXIII-b) can be converted into an intermediate of formula (XLIV) by reaction with a suitable acid, such as hydrochloric acid or hydrobromic acid and the like or mixtures thereof, in the presence of a suitable solvent, e.g. water.

Intermediates of formula (XXXIII-a) or (XXXIII-b), wherein in the definition of Q_1, the X^1 or X^2 moieties in the radicals of formula (b-1) to (b-8) represent NH, said Q_1 being represented by Q_{1c}-NH, and said intermediates by formula (XXXIII-a-1) or (XXXIII-b-1), can be prepared by reacting an intermediate of formula (XLV-a) or (XLV-b), wherein W_5 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, with an intermediate of formula (XLVI).

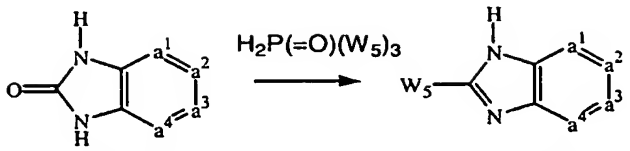


(XLV-a) (XLVI) (XXXIII-a-1)

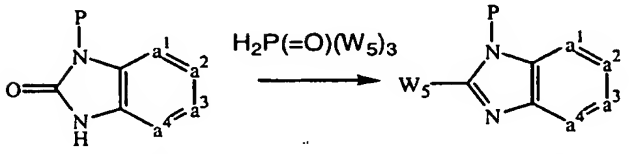


(XLV-b) (XLVI) (XXXIII-b-1)

Intermediates of formula (XLV-a) or (XLV-b) can be prepared by reacting an intermediate of formula (XLVII-a) or (XLVII-b) with $H_2P(=O)(W_5)_3$ in the presence of a suitable acid, e.g. hydrochloric acid.

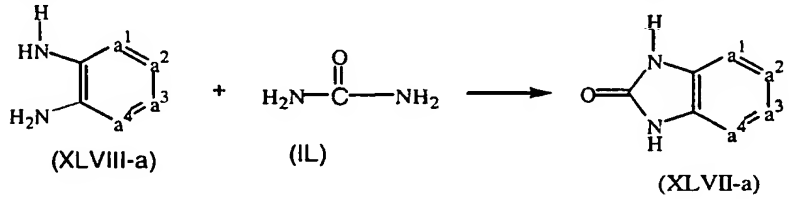


(XLVII-a) (XLV-a)

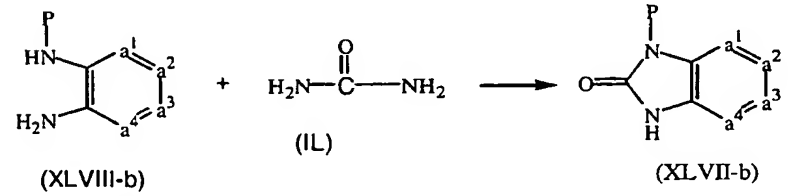


(XLVII-b) (XLV-b)

Intermediates of formula (XLVII-a) or (XLVII-b) can be prepared by reacting an intermediate of formula (XLVIII-a) or (XLVIII-b) with an intermediate of formula (IL).

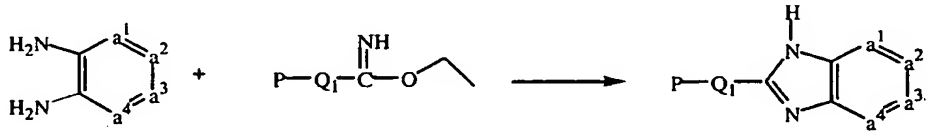


(XLVIII-a) (IL) (XLVII-a)



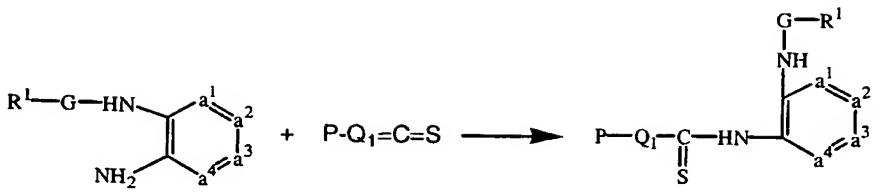
(XLVIII-b) (IL) (XLVII-b)

Intermediates of formula (XXXIII-a) can also be prepared by reacting an intermediate of formula (XLVIII-a) with P-Q_1-C(=NH)-O-CH_2-CH_3 in a reaction-inert solvent, such as an alcohol.



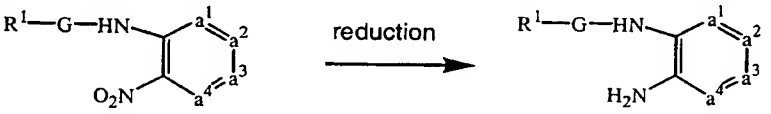
(XLVIII-a) (XXXIII-a)

Intermediates of formula (XXXV) can be prepared by reacting an intermediate of formula (L) with an intermediate of formula P-Q_1=C=S, which is synthesized according to the procedures described in EP 0005318, in a reaction-inert solvent, such as an alcohol, e.g. ethanol. To increase the reaction rate, the reaction may be performed at elevated temperatures.



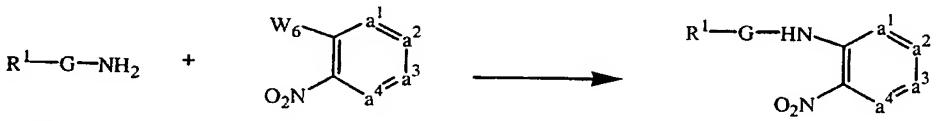
(L) (XXXV)

Intermediates of formula (L) can be obtained by reducing an intermediate of formula (LI) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst, e.g. Raney Nickel.



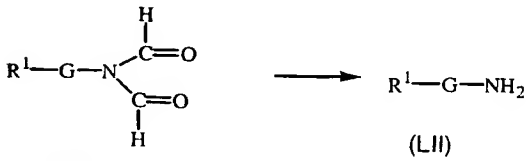
(LI) (L)

Intermediates of formula (LI) can be prepared by reacting an intermediate of formula (LII) with an intermediate of formula (LIII), in which W_6 represents a suitable leaving group, such as a halo atom, e.g. chloro. This reaction may be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



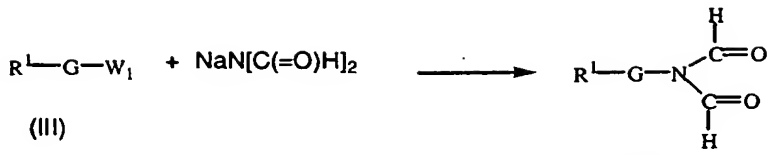
(LII) (LIII) (LI)

Intermediates of formula (LII) can be prepared by reacting an intermediate of formula (LIV) with a suitable acid, such as hydrochloric acid, in the presence of a suitable solvent, e.g. an alcohol, e.g. ethanol.



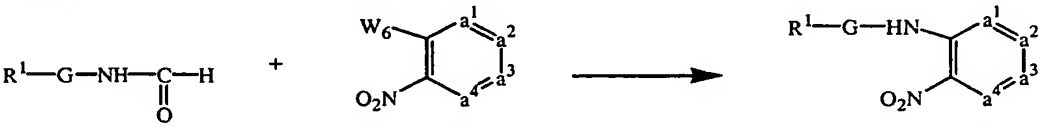
(LIV)

Intermediates of formula (LIV) can be prepared by reacting an intermediate of formula (III) with $NaN[C(=O)H]_2$.



(III) (LIV)

Intermediates of formula (LI) can also be prepared by reacting an intermediate of formula (LIII) with an intermediate of formula (LV) (J. Org. Chem., 25, p 1138, 1960) in a reaction-inert solvent, e.g. *N,N*-dimethylformamide, in the presence of an appropriate base, e.g. sodium hydride.

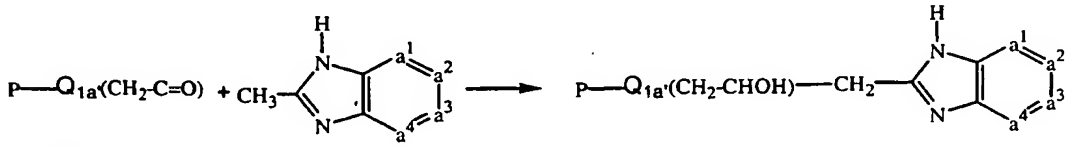


(LV) (LIII) (LI)

Intermediates of formula (XXXVI) can be prepared by dehydrating an intermediate of formula (LVI) with a suitable acid, such as sulfuric acid.

(LVI) (XXXVI)

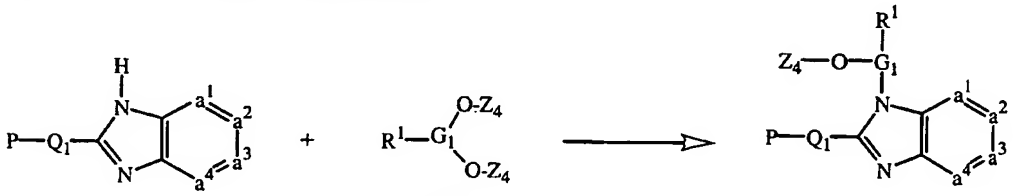
Intermediates of formula (LVI) wherein, in the definition of Q_{1a}, the X^1 or X^2 moieties are CH_2, said Q_{1a} being represented by $Q_{1a'}$, and said intermediates being represented by formula (LVI-a), can be prepared by reacting a carbonyl moiety of formula (LVII) with an intermediate of formula (LVIII) in the presence of *N,N*-diisopropylamine and butyl lithium, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



(LVII) (LVIII) (LVI-a)

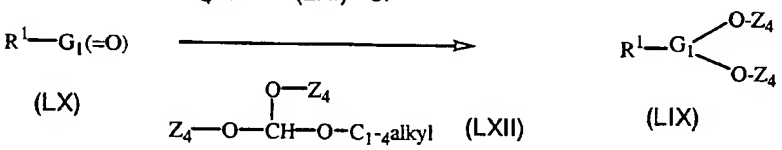
Intermediates of formula (IV), wherein G is C_{1-10}alkanediyl substituted with C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, $HO(-CH_2CH_2O)_n-$, C_{1-6}alkyloxy$(-CH_2CH_2O)_n-$, or arylC_{1-6}alkyloxy$(-CH_2CH_2O)_n-$, said group of substituents being represented by O-Z_4, said G being represented by Z_4-O-G_1, and said intermediates being represented by formula (IV-f), can be prepared by reacting an intermediate of formula (XXXIII-a), with an intermediate of formula (LIX), optionally in the presence of a suitable acid, such as p-toluenesulfonic acid and the like, and optionally in the presence of a suitable solvent,

such as *N,N*-dimethylacetamide. To increase the reaction rate, the reaction may be carried out at elevated temperatures.



(XXXIII-a) (LIX) (IV-f)

Intermediates of formula (LIX) can be prepared by reacting an intermediate of formula (LX) with a reagent of formula (LXI) or (LXII) in a reaction-inert solvent, such as an alcohol, or toluene, in the presence of an acid, e.g. 4-methylbenzenesulphonic acid.

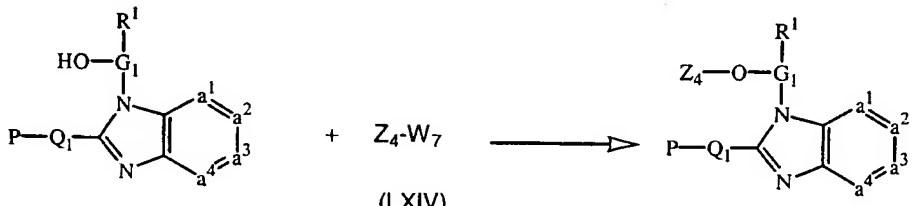


(LX) (LXII) (LIX)

Intermediates of formula (LX) can be prepared by oxidizing an intermediate of formula (LXIII) with a suitable oxidizing agent, e.g. MnO_2, in a reaction-inert solvent, such as methylene chloride.

(LXIII) (LX)

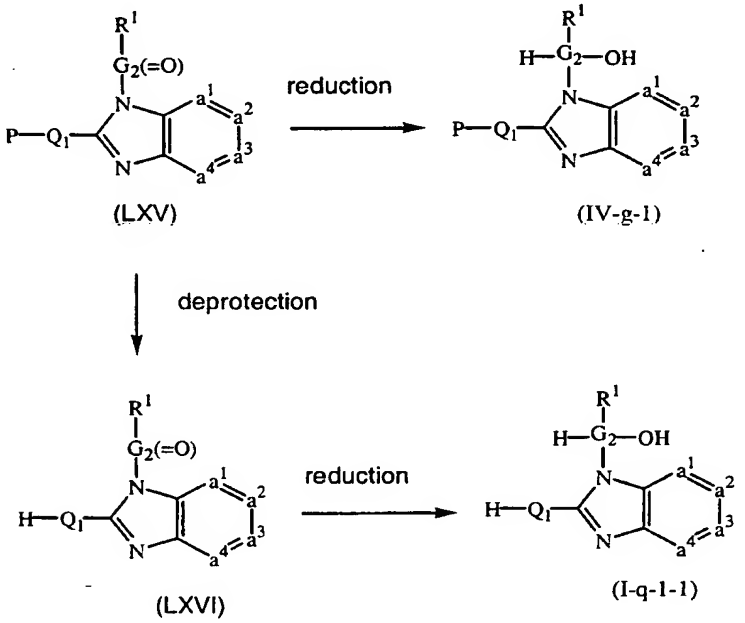
Intermediates of formula (IV-f) can also be prepared by reacting an intermediate of formula (IV) wherein G is C_{1-10}alkanediyl substituted with hydroxy, said G being represented by G_1-OH, and said intermediates being represented by formula (IV-g), with an intermediate of formula (LXIV), wherein W_7 is a suitable leaving group, such as a halo atom, e.g. iodo, in the presence of a suitable base, e.g. sodium hydride, in a reaction-inert solvent, e.g. tetrahydrofuran.



(IV-g) (LXIV) (IV-f)

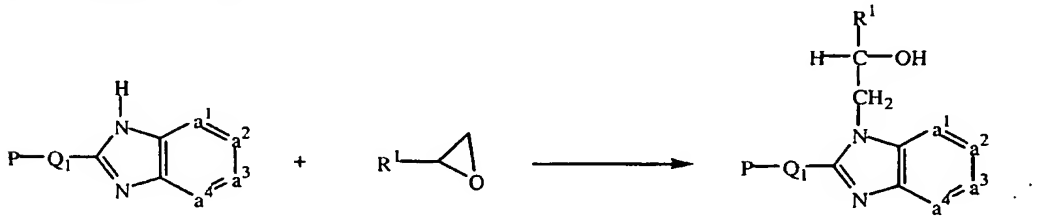
Intermediates of formula (IV-g), wherein the carbon atom of G_1 carrying the hydroxy, also carries a hydrogen atom, said G_1-OH being represented by H-G_2-OH, and said intermediates being represented by formula (IV-g-1), can be prepared by reducing an

intermediate of formula (LXV) in the presence of a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, such as an alcohol, tetrahydrofuran or a mixture thereof. Intermediates of formula (LXV) can also first be deprotected, e.g. in the presence of a suitable acid, such as hydrochloric acid and the like, resulting in intermediates of formula (LXVI), followed by a reduction, resulting in a compound of formula (I-q-1) wherein Q represents H-Q_1, said compounds being represented by formula (I-q-1-1).



(LXV) (IV-g-1) (LXVI) (I-q-1-1)

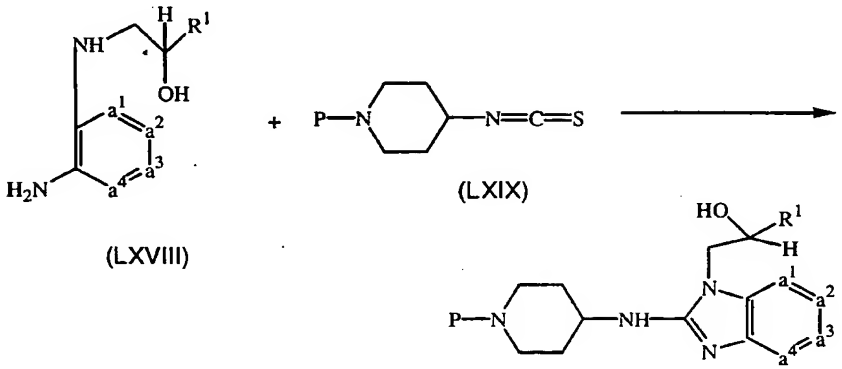
Intermediates of formula (IV), wherein G is ethyl substituted with hydroxy, said intermediates being represented by formula (IV-g-2) can also be prepared by reacting an intermediate of formula (XXXIII-a) with an intermediate of formula (LXVII) in the presence of a suitable base, such as sodium hydride, in a reaction-inert solvent, such as *N,N*-dimethylformamide.



(XXXIII-a) (LXVII) (IV-g-2)

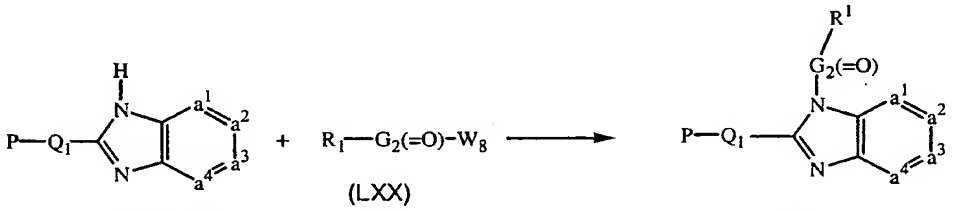
A subgroup of intermediates of formula (IV-g-2), represented by formula (IV-g-2-1), can also be prepared by reacting an intermediate of formula (LXVIII) with an

intermediate of formula (LXIX) in the presence of 1,3-dicyclohexylcarbodiimide, in a reaction-inert solvent, e.g. toluene.



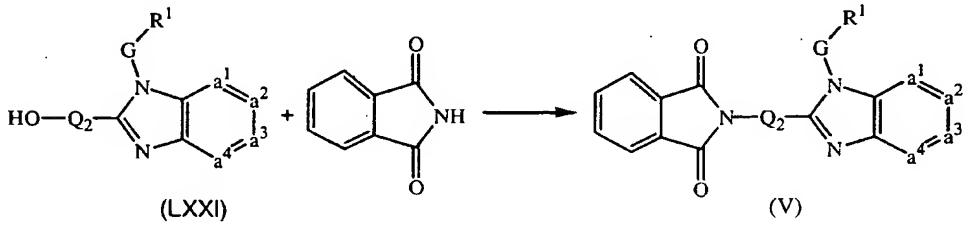
(LXVIII) (LXIX) (IV-g-2-1)

Intermediates of formula (LXV) can be prepared by reacting an intermediate of formula (XXXIII-a) with an intermediate of formula (LXX), wherein W_8 is a suitable leaving group, such as a halo atom, e.g. bromo, in the presence of a suitable base, e.g. sodium hydride, in a reaction-inert solvent, e.g. *N,N*-dimethylformamide.



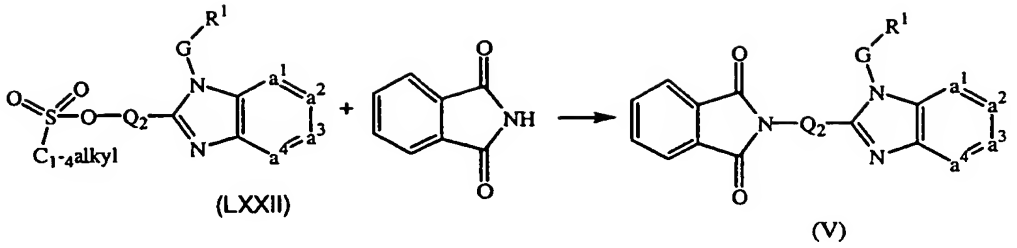
(XXXIII-a) (LXX) (LXV)

Intermediates of formula (V) can be prepared by reacting an intermediate of formula (LXXI) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of triphenylphosphine and diethyl azodicarboxylate.



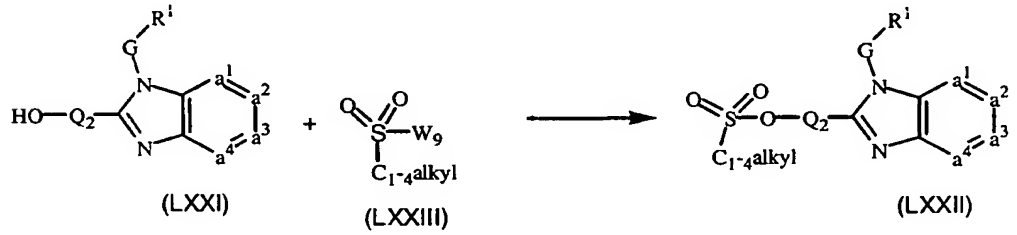
(LXXI) (V)

Intermediates of formula (V) may also be prepared by reacting an intermediate of formula (LXXII) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of a suitable base, such as sodium hydride, and a suitable solvent, such as *N, N* -dimethylformamide.



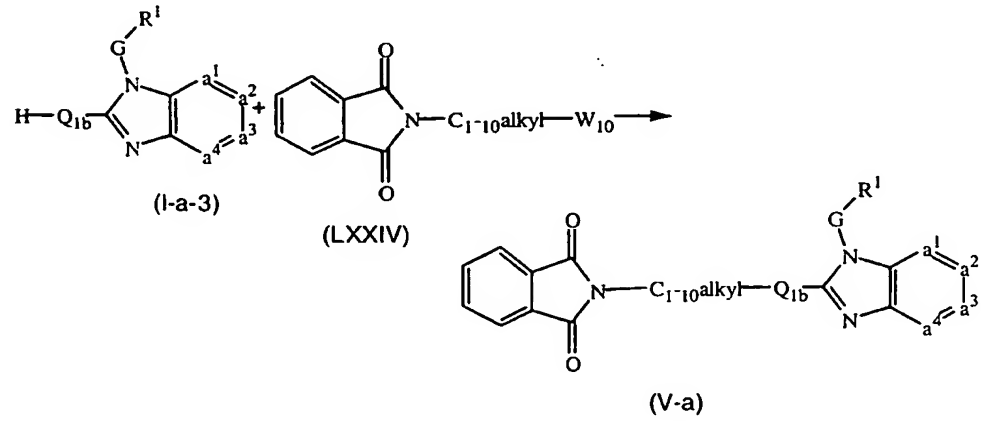
(LXXII) (V)

Intermediates of formula (LXXII) can be prepared by reacting an intermediate of formula (LXXI) with an intermediate of formula (LXXIII), wherein W_9 represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as *N*, *N* -diethyl-ethanamine, and a suitable solvent, such as methylene chloride.



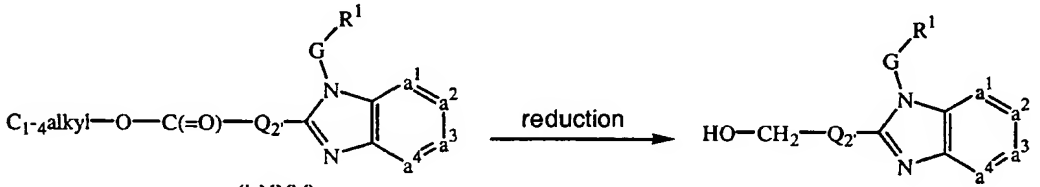
(LXXI) (LXXIII) (LXXII)

Intermediates of formula (V), wherein in the definition of Q_2, R^2 is C_{1-10}alkyl, said Q_2 being represented by C_{1-10}alkyl-Q_{1b}, and said intermediates by formula (V-a), can be prepared by reacting a compound of formula (I-a-3) with an intermediate of formula (LXXIV), wherein W_{10} is a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as dipotassium carbonate, and a suitable solvent, such as acetonitrile.



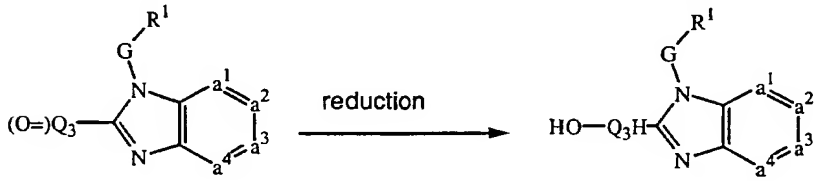
(I-a-3) (LXXIV) (V-a)

Intermediates of formula (LXXI) wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, also carries two hydrogen atoms, said HO-Q_2 being represented by HO-CH_2-$Q_{2'}$, and said intermediates being represented by formula (LXXI-a), can be prepared by reducing an intermediate of formula (LXXV) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



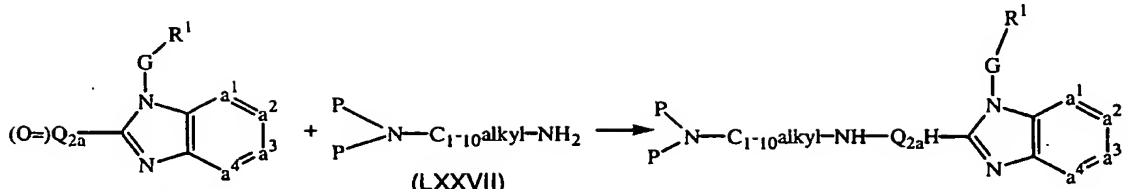
(LXXV) (LXXI-a)

Intermediates of formula (LXXI), wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, carries also at least one hydrogen, said HO-Q_2 being represented by HO-Q_3H, and said intermediates being represented by formula (LXXI-b), can be prepared by reducing an intermediate of formula (IX) with a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. an alcohol.



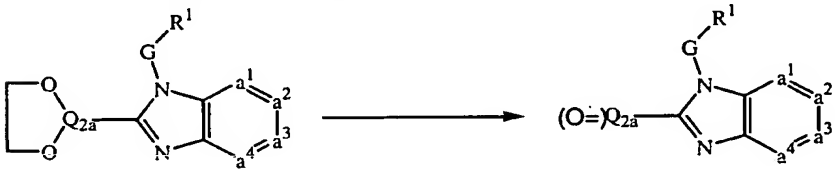
(IX) (LXXI-b)

Intermediates of formula (VI) wherein, in the definition of Q_2, R^2 is C_{1-10}alkyl substituted with $N(P)_2$ and the carbon atom adjacent to the nitrogen atom carrying the R^2 substituent carries also at least one hydrogen atom, said Q_2 being represented by $(P)_2N$-C_{1-10}alkyl-NH-Q_{2a}H, and said intermediates being represented by formula (VI-a), can be prepared by reductive amination of an intermediate of formula (LXXVI) with an intermediate of formula (LXXVII) in the presence of a suitable reductive agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like, and optionally in the presence of a suitable catalyst poison, such as a thiophene solution. A suitable solvent in this reaction is a reaction-inert solvent, such as an alcohol.



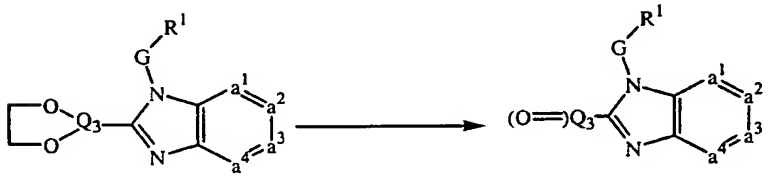
(LXXVI) (LXXVII) (VI-a)

Intermediates of formula (LXXVI) can be prepared by deprotecting an intermediate of formula (LXXVIII) in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, e.g. water.



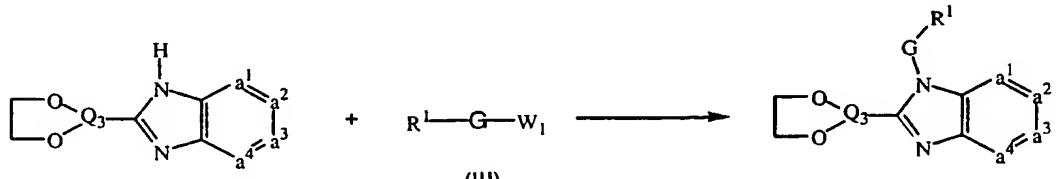
(LXXVIII) (LXXVI)

Intermediates of formula (IX) may be prepared by deprotecting an intermediate of formula (LXXIX) in the presence of a suitable acid, e.g. hydrochloric acid and the like.



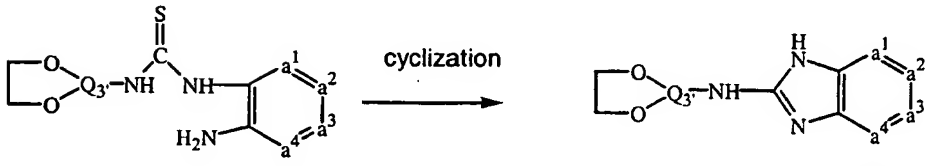
(LXXIX) (IX)

Intermediates of formula (LXXIX) can be prepared by reacting an intermediate of formula (LXXX) with an intermediate of formula (III) in the presence of a suitable base, e.g. dipotassium carbonate, in a suitable reaction-inert solvent, e.g. acetonitrile.



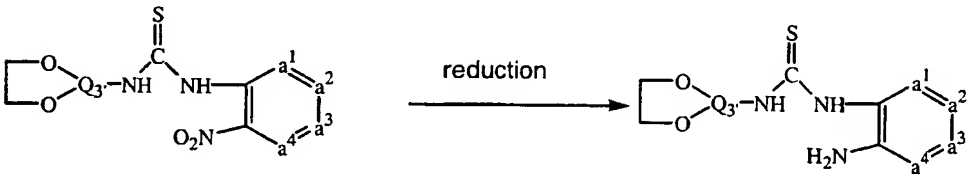
(LXXX) (III) (LXXIX)

Intermediates of formula (LXXX) wherein, in the definition of Q_3, the X^1 or X^2 moiety of the radicals of formula (b-1) to (b-8) represent NH, said Q_3 being represented by $Q_{3'}$-NH, and said intermediates being represented by formula (LXXX-a), may be prepared by cyclizing an intermediate of formula (LXXXI) in the presence of mercury oxide and sulphur, in a suitable reaction-inert solvent, e.g. an alcohol.



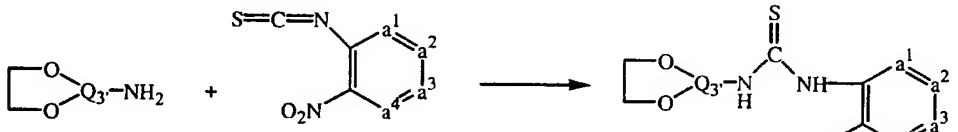
(LXXXI) (LXXX-a)

Intermediates of formula (LXXXI) can be prepared by reducing an intermediate of formula (LXXXII) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal and the like, in a suitable solvent, e.g. a mixture of ammonia in alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.



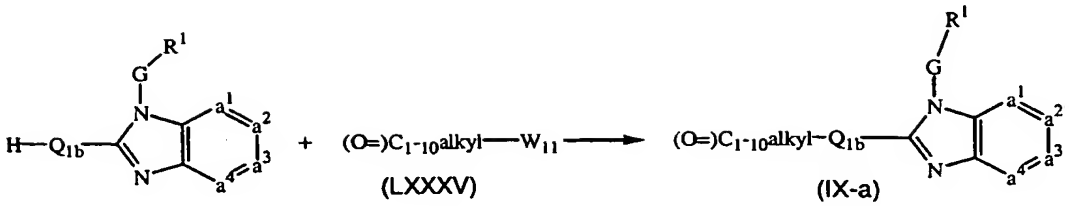
(LXXXII) (LXXXI)

Intermediates of formula (LXXXII) can be prepared by reacting an intermediate of formula (LXXXIII) with an intermediate of formula (LXXXIV) in a suitable reaction-inert solvent, e.g. ethanol.

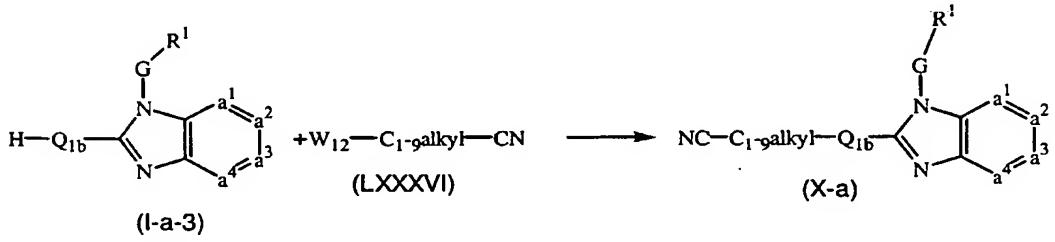


(LXXXIII) (LXXXIV) (LXXXII)

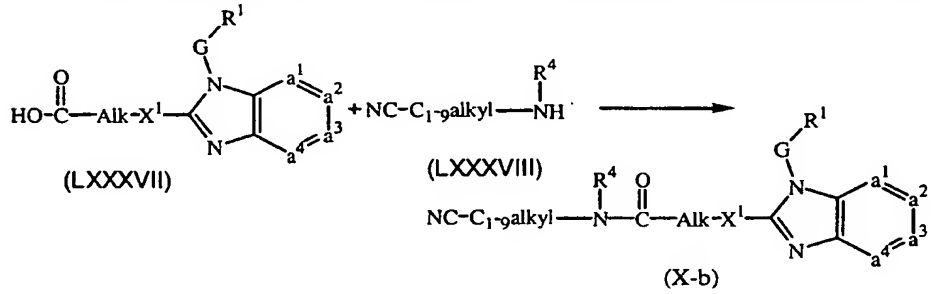
Intermediates of formula (IX), wherein, in the definition of Q_3, R^2 comprises C_{1-10}alkyl, said Q_3 being represented by C_{1-10}alkyl-Q_{1b}, and said intermediates being represented by formula (IX-a), can be prepared by reacting a compound of formula (I-a-3) with a reagent of formula (LXXXV), wherein (O=)C_{1-10}alkyl represents a carbonyl derivative of C_{1-10}alkyl and wherein W_{11} is a suitable leaving group, such as a halo atom, e.g. bromo, in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



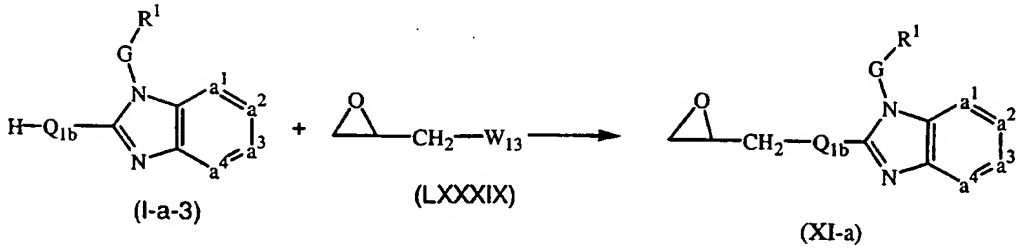
Intermediates of formula (X) wherein Q_4 comprises C_{1-9}alkyl, said Q_4 being represented by C_{1-9}alkyl-Q_{1b}, and said intermediates being represented by formula (X-a), can be prepared by reacting a compound of formula (I-a-3) with a reagent of formula (LXXXVI) wherein W_{12} represents a suitable leaving group, such as a halo atom, e.g. chloro, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, in the presence of a suitable base, e.g. dipotassium carbonate, sodium bicarbonate and the like.



Intermediates of formula (X), wherein NC-Q_4 represents NC-(C_{1-9}alkyl)(R^4)N-C(=O)-Alk-X^1, said intermediates being represented by formula (X-b), can be prepared by reacting an intermediate of formula (LXXXVII) with an intermediate of formula (LXXXVIII) in the presence of di-1*H*-imidazol-2-yl-methanone, a suitable base, such as *N*, *N* -diethyl-ethanamine, and a suitable solvent, such as methylene chloride.

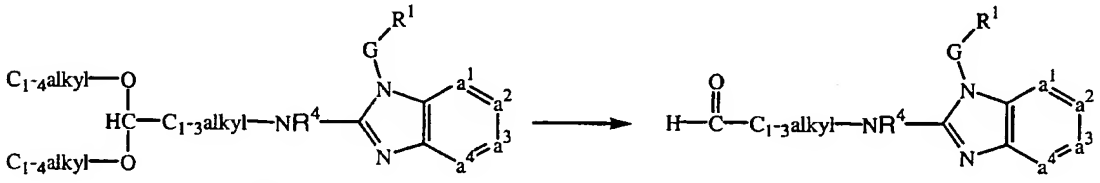


Intermediates of formula (XI), wherein Q_4 represents Q_{1b}, said intermediates being represented by formula (XI-a), can be prepared by reacting a compound of formula (I-a-3) with an intermediate of formula (LXXXIX), wherein W_{13} represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as disodium carbonate, and in the presence of a suitable solvent, such as 3-methyl-2-butanone.



(I-a-3) (LXXXIX) (XI-a)

Intermediates of formula (XIX) can be prepared by reacting an intermediate of formula (XC) with a suitable acid, such as hydrochloric acid.



(XC) (XIX)

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections

brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly RSV infection.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical

media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated

tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

The following examples are intended to illustrate the present invention.

Experimental part

Hereinafter, "DMF" is defined as *N*,*N*-dimethylformamide, "DIPE" is defined as diisopropyl ether.

A. Preparation of the intermediate compounds

Example A1

a) Sodium methoxide (0.2 mol) was added to a mixture of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide (0.1 mol) in methanol (389ml), the mixture

was cooled on an ice bath and stirred for 2 hours.

Di-tert-butyldicarbonate (0.1mol) was added to a cooled mixture on an ice bath and then stirred for 18 hours at room temperature. The mixture was evaporated and suspended in water/DIPE. The residue was filtered off, washed with water/DIPE and dried. The residue was boiled up in CH_3OH, yielding 17.46g (55.2%) of 1,1-dimethylethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 249.4°C (interm. 1).

b) A mixture of intermediate (1) (0.05 mol), 2-(chloromethyl)quinoline monohydrochloride (0.055 mol) and sodium carbonate (0.075 mol) in DMF (250ml) was stirred at 55°C overnight. The solvent was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3 and 95/5). The pure fractions were collected and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried, yielding 13.5g (59%) of 1,1-dimethylethyl 4-[[1-(quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 2).

Example A2

a) A mixture of 5,6,7,8-tetrahydro-2(1*H*)-quinoxalinone in phosphoryl chloride (200ml) was stirred and refluxed for 3 hours. The solvent was evaporated. The residue was taken up in ice and CH_2Cl_2. The mixture was basified with NH_4OH. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 34g (86%) of 2-chloro-5,6,7,8-tetrahydroquinoxaline (interm. 3).

b) A mixture of intermediate (3), 1-bromo-2,5-pyrolidinedione (0.116 mol) and dibenzoyl peroxide (1.3g) in tetrachloromethane (400ml) was stirred and refluxed for 35 minutes, brought to room temperature and then filtered. The reaction was carried out again using the same quantities. The residues were combined. The solvent was evaporated. The residue (60g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/5; 15-35 µm). Two pure fractions were collected and their solvents were evaporated, yielding 25 g (43%) of (±)-5-bromo-2-chloro-5,6,7,8-tetrahydroquinoxaline (interm. 4) and 12 g (21%) of (±)-8-bromo-2-chloro-5,6,7,8-tetrahydroquinoxaline.

c) A dispersion of sodium hydride in mineral oil (60%) (0.0518 mol) was added portionwise at 5°C under N_2 flow to a mixture of intermediate (1) (0.0471 mol) in DMF (200ml). The mixture was stirred at 5°C/10°C for 1 hour. A solution of intermediate (4) (0.0565 mol) in DMF (50ml) was added dropwise. The mixture was stirred at room temperature for 3 hours and poured out into H_2O. The precipitate was

filtered off and taken up in CH_2Cl_2. The organic solution was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (32g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 95/5/0.1; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 13.3g (58%) of (±)-1,1-dimethylethyl 4-[[1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 5).

Example A3

a) 2,3-Butanedione (0.0776 mol) was added at room temperature to a solution of sodium pyrosulfite (0.1 mol) in water (75ml). The mixture was heated to 70°C and then added to a solution of ethyl 2,3-diaminobenzoate (0.0776 mol) in water (75ml). The mixture was stirred at 100°C for 12 hours, cooled, basified with K_2CO_3 10% and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (17.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 93/7; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 12g (67%) of ethyl 2,3-dimethyl-5-quinoxalinecarboxylate (interm. 6).

b) Lithium chloride (0.6 mol) was added portionwise at 80°C to a mixture of intermediate (6) (0.06 mol) and potassium tetrahydroborate (0.6 mol) in tetrahydrofuran (300ml). The mixture was stirred at 80°C for 5 hours, cooled, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 10.5g (91%) of (±)-1,2,3,4-tetrahydro-2,3-dimethyl-5-quinoxaline-methanol (interm. 7).

c) MnO_2 (100g) was added portionwise at room temperature to a mixture of intermediate (7) (0.0546 mol) in dichloromethane (500ml). The mixture was stirred at room temperature overnight, filtered over celite, washed with CH_2Cl_2 and the filtrate was evaporated. The product was used without further purification, yielding 7.8g (77%) of 2,3-dimethyl-5-quinoxalinecarboxaldehyde (interm. 8).

d) Sodium tetrahydroborate (0.084 mol) was added portionwise at 5°C to a mixture of intermediate (8) (0.042 mol) in methanol (100ml). The mixture was stirred at 5°C for 30 minutes, hydrolized cold and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 6.7g (85%) 2,3-dimethyl-5-quinoxalinemethanol (interm. 9).

e) Thionyl chloride (0.045 mol) was added dropwise at 5°C to a mixture of intermediate (9) (0.03 mol) in dichloromethane (50ml). The mixture was stirred at room temperature for 2 hours, poured out on ice and K_2CO_3 10%. The organic layer was separated, washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was

evaporated. The product was used without further purification, yielding 6.2g (quant.) of 5-(chloromethyl)-2,3-dimethyl-quinoxaline (interm. 10).

f) A dispersion of sodium hydride in mineral oil (60%) (0.021 mol) was added portionwise at 5°C under N_2 flow to a mixture of intermediate (1) (0.02 mol) in DMF (30ml). The mixture was stirred at 5°C under N_2 flow for 1 hour. A solution of intermediate (10) (0.03 mol) in a small amount of DMF was added dropwise at 5°C. The mixture was stirred at room temperature under N_2 flow for 2 hours, hydrolized and extracted with EtOAc. The organic layer was separated, washed several times with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (12.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97.5/2.5/0.1; 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding 7.8g (80%) of 1,1-dimethylethyl 4-[[1-[(2,3-dimethyl-5-quinoxalinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 11).

Example A4

8-Bromo-2-methylquinoline (0.0675 mol) was added portionwise at -70°C under N_2 flow to a mixture of a solution of butyllithium in hexane (1.6M) (0.135 mol) in tetrahydrofuran (300ml) and diethyl ether (300ml). The mixture was stirred for 30 minutes. A solution of DMF (0.405 mol) in tetrahydrofuran (100ml) was added quickly. The mixture was cooled to -70°C and stirred for 15 minutes. Ethanol (70ml) and a NH_4Cl solution 10% were added. The mixture was brought to room temperature and stirred for 15 minutes. NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 15g (>100%) of 2-methyl-8-quinolinecarboxaldehyde (interm. 12).

Example A5

a) A mixture of 3-methoxy-2-methylquinoline (0.081 mol) in trifluoro-acetic acid (150ml) was hydrogenated at room temperature under a 3-4 bar pressure for 48 hours with palladium on activated carbon (2g) as a catalyst. After uptake of hydrogen (2 equiv.), the catalyst was filtered through celite and washed with H_2O. The filtrate was basified with a concentrated NH_4OH solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 14.3g (quant.) of 5,6,7,8-tetrahydro-3-methoxy-2-methylquinoline (interm. 13).

b) 3-Chlorobenzenecarboperoxoic acid (0.1 mol) was added portionwise at 5°C to a mixture of intermediate (13) (0.067 mol) in dichloromethane (300ml). The mixture was stirred at room temperature overnight, basified with K_2CO_3 10% and separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic

layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 13.7g (quant.) of 5,6,7,8-tetrahydro-3-methoxy-2-methylquinoline, 1-oxide (interm. 14).

c) A mixture of intermediate (14) (0.067 mol) in acetic anhydride (100ml) was stirred at 90°C for 1 hour, poured out on ice and basified with NaOH 3N. CH_2Cl_2 was added. The organic layer was separated, washed with a diluted NaOH solution, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 16.8g (quant.) of 5,6,7,8-tetrahydro-3-methoxy-2-quinolinemethanol acetate (ester) (interm. 15).

d) A mixture of intermediate (15) (0.067 mol) and sodium hydroxide (13g) in methanol (60ml) was stirred and refluxed for 20 minutes, poured out on ice and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 12.3g (95%) of 5,6,7,8-tetrahydro-3-methoxy-2-quinolinemethanol (interm. 16).

In a similar way was also prepared (±)-5,6,7,8-tetrahydro-2-methyl-8-quinolinol (interm. 17).

Example A6

Phosphorus tribromide (0.0105 mol) was added dropwise at 0°C/5°C under N_2 flow to a mixture of (±)-5,6,7,8-tetrahydro-2-methyl-8-quinolinol (intermediate 17) (0.03 mol) in toluene (20ml). The mixture was brought to room temperature and stirred at room temperature overnight. Ice water was added. The mixture was basified with a concentrated NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 2g (29%) of (±)-8-bromo-5,6,7,8-tetrahydro-2-methylquinoline (interm. 18).

Example A7

a) A mixture of *N*-2,6-dimetyl-2,3-pyridinediamine (0.122 mol) in trifluoro-acetic acid (250ml) was stirred and refluxed for 6 hours and brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 and K_2CO_3 10%. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (32g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 97/3; 20-45 µm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in petroleum ether. The precipitate was filtered off and dried, yielding 15g of residue (fraction 1). The mother layer was evaporated. The residue was combined with 14.1g of fraction 1, yielding 28.9 g of 1,6-dimethyl-2-(trifluoromethyl)-1*H*-imidazo[4,5-b]pyridine; mp. 100°C (interm. 19).

b) 1-Bromo-2,5-pyrolidinedione (0.0735 mol) and dibenzoyl peroxide (1.5g) were added at room temperature to a solution of intermediate (19) (0.07 mol) in tetrachloromethane (450ml). The mixture was stirred and refluxed for 7 hours, then brought to room temperature and filtered. The reaction was carried out again using the same quantities. The mixtures were combined. The solvent was evaporated. The residue (50g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 and 98/2; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 20.2g (49%) of 6-(bromomethyl)-1-methyl-2-(trifluoromethyl)-1*H*-imidazo[4,5-b]pyridine (interm. 20).

c) A mixture of ethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidine-carboxylate (0.0464 mol), intermediate (20) (0.051 mol) and potassium carbonate (0.1392 mol) in acetonitrile (250ml) was stirred and refluxed for 90 minutes and then brought to room temperature. Water was added and the mixture was extracted twice with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 23g (>100%) of ethyl 4-[[1-[[1-methyl-2-(trifluoromethyl)-1*H*-imidazo[4,5-b]pyridin-6-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 21).

Example A8

A mixture of ethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidine-carboxylate (0.0289 mol), 7-chloro-6,7-dihydro-5*H*-cyclopenta[b]pyridine (0.0289 mol) and potassium carbonate (0.0867 mol) in acetonitrile (250ml) was stirred and refluxed for 48 hours and then brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined, poured out into H_2O and extracted with EtOAc. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (25g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97/3/0.5; 20-45 µm). Two fractions were collected and their solvents were evaporated, yielding 8g of ethyl 4-[[1-(6,7-dihydro-5*H*-1-pyrindin-7-yl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 22).

Example A9

a) A dispersion of sodium hydride in mineral oil (0.261 mol) was added portionwise at room temperature under N_2 flow to a mixture of *N*-8-quinolinylformamide (0.174 mol) in DMF (500ml). The mixture was stirred at room temperature for 1 hour. A solution of 1-chloro-2-nitrobenzene (0.53 mol) in DMF (200ml) was added dropwise. The mixture was stirred at 140°C for 12 hours and then brought to room temperature. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was

separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (110g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 80/20; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 9.8g (21%) of *N*-(2-nitrophenyl)-8-quinolinamine (interm. 23).

b) A mixture of 6-quinolinemethanamine (0.074 mol), 2-chloro-3-nitropyridine (0.0888 mol) and potassium carbonate (0.185 mol) in acetronitrile (200ml) was stirred and refluxed for 5 hours and then cooled to room temperature. EtOAc and H_2O were added. The mixture was extracted with HCl 3N. The aqueous layer was basified with K_2CO_3 solid and extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 17.8g (84%) of *N*-(3-nitro-2-pyridinyl)-8-quinolinemethanamine (interm. 24).

Example A10

a) A mixture of intermediate (24) (0.064 mol) in methanol (200ml) was hydrogenated under a 3 bar pressure for 2 hours with Raney nickel (10g) as a catalyst. After uptake of hydrogen (3 equiv), the catalyst was filtered through celite and the filtrate was evaporated, yielding 14.8g (93%) of *N2*-(8-quinolinylmethyl)-2,3-pyridinediamine (interm. 25).

b) A mixture of intermediate (25) (0.059 mol) and ethyl 4-isothiocyanato-1-piperidine-carboxylate (0.059 mol) in methanol (150ml) was stirred and refluxed for 4 hours and brought to room temperature. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3; 20-45 µm). The desired fractions were collected and the solvent was evaporated, yielding 10.5g (37%) of ethyl 4-[[[[2-[(8-quinolinylmethyl)amino]-3-pyridinyl]amino]sulfinyl]-amino]-1-piperidine-carboxylate (interm. 26)

c) A mixture of intermediate (26) (0.026 mol), mercury(II) oxide (0.052 mol) and sulfur (0.2g) in ethanol (120ml) was stirred and refluxed for 2 hours, brought to room temperature and filtered over celite. The filtrate was evaporated, yielding 8.7g (96%) of 4-[[1-(8-quinolinylmethyl)-1*H*-imidazo[4,5-b]pyridin-2-yl]amino]-1-piperidine-carboxylate (interm. 27).

Example A11

a) A mixture of 8-quinolinecarboxaldehyde (0.092 mol) and 4-methylbenzenesulfonic acid (0.3g) in 2-ethoxyethanol (110ml) was stirred and refluxed for 24 hours using a Dean Stark apparatus. The solvent was evaporated. The reaction was carried out again using the same quantities. The residues were combined and taken up in CH_2Cl_2. The organic solution was washed with K_2CO_3 10% and decanted. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (41g) was

purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding 20g (34%) of 8-[bis(2-ethoxyethoxy)methyl]quinoline (interm. 28).

b) A mixture of 8-quinolinecarboxaldehyde (0.248 mol), triethoxymethane (0.4464 mol) and 4-methylbenzenesulfonic acid (4g) in ethanol (250ml) was stirred and refluxed for 1 hour, brought to room temperature, poured out into K_2CO_3 10% and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 48.5g (80%) of 8-(diethoxymethyl)-quinoline (interm. 29).

c) A mixture of 2-quinolinecarboxaldehyde (0.08 mol) and 4-methylbenzenesulfonic acid (0.25g) in ethanol (100ml) was stirred and refluxed for 48 hours and brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with K_2CO_3 10% and with H_2O, then dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without further purification, yielding 32.5g of 2-(diethoxymethyl)quinoline (interm. 30).

Example A12

Intermediate (1) (0.0377 mol) and intermediate (29) (0.0755 mol) were heated at 160°C for 1 hour and then purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-35 µm). The pure fractions were collected and the solvent was evaporated, yielding 15g (79%) of (±)-1,1-dimethylethyl 4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (interm. 31).

Example A13

4-Methylbenzenesulfonyl chloride (0.2222 mol) was added portionwise at 10°C to a mixture of 1,1-dimethylethyl [1-(hydroxymethyl)-2-methylpropyl]carbamic acid (ester) (0.202 mol) in pyridine (65ml). The mixture was stirred at 10°C for 2 hours. H_2O (75ml) was added at 10°C. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated, yielding 49g (68%) of (±)-1,1-dimethylethyl [1-[[[(4-methylphenyl)sulfonyl]oxy]methyl]-2-methylpropyl]carbamate; mp. 85°C(interm. 32).

Example A14

a) A mixture of compound (33) (0.0347 mol), 1-bromo-3-methyl-2-butanone (0.052 mol) and potassium carbonate (0.104 mol) in acetonitrile (255ml) was stirred and refluxed for 2 hours and filtered. The filtrate was evaporated. The residue was taken up in H_2O and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was

used without further purification, yielding 16.84g of (±)-1-[4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (interm. 34) (quant.).

In a similar way were also prepared :

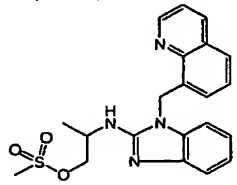
1-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]-3-methyl-2-butanone;

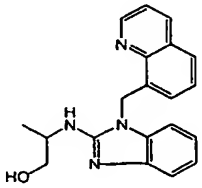
1-[4-[[1-(8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone; and

1-[4-[[1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone.

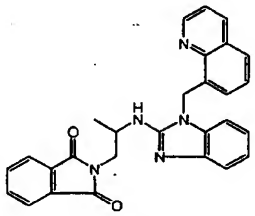
b) A mixture of intermediate (34) (0.036 mol) in methanol (200ml) was stirred at 10°C. Sodium tetrahydroborate (0.04 mol) was added portionwise. The mixture was stirred for 90 minutes. H_2O was added. The solvent was evaporated. The residue was extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 17g (96%) of (±)-4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-alpha-(1-methylethyl)-1-piperidineethanol (interm. 35).

c) Diethyl azodicarboxylate (0.015 mol) was added dropwise at 0°C under N_2 flow to a solution of intermediate (35) (0.01 mol), phthalimide (0.015 mol) and triphenyl-phosphine (0.015 mol) in tetrahydrofuran (100ml). The mixture was stirred at room temperature for 2 hours. EtOAc was added. The mixture was extracted with HCl 3N and separated into its layers. The aqueous layer was washed twice with EtOAc, basified with K_2CO_3 solid and extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.2; 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding 2.3g (30%) of (±)-2-[2-[4-[[1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methylbutyl]-1*H*-isoindole-1,3(2*H*)dione (interm.

d) Preparation of intermediate  (80)

A solution of  (0.024 mol) (prepared according to A14b)

and Et_3N (0.072 mol) in CH_2Cl_2 (100ml) was cooled to 0°C under N_2 flow. A mixture of methanesulfonyl chloride (0.036 mol) in CH_2Cl_2 (a small amount) was added dropwise. The mixture was allowed to cool to room temperature while stirring for 3 hours. Water was added. The mixture was decanted. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 8.5g of intermediate (80) (86%).

e) Preparation of intermediate  (81)

A solution of 1*H*-isoindole-1,3(2*H*)-dione (0.0828 mol) in DMF (80ml) was cooled to 10°C. NaH 60% in oil (0.0828 mol) was added portionwise. The mixture was allowed to cool to room temperature while stirring for 1 hour. A mixture of intermediate (80) (0.0207 mol) (prepared according to A14d) in DMF (a small amount) was added dropwise. The mixture was stirred at room temperature for 1.5 hours, at 60°C for 5 hours and at room temperature for the weekend. The residue (9.6g) was crystallized from diethyl ether and CH_3CN. The precipitate was filtered off and dried, yielding 4g of intermediate (81) (42%).

Example A15

a) A mixture of 1-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]-3-methyl-2-butanone (0.03 mol) and benzenemethanamine (0.09 mol) in methanol (200ml) was hydrogenated at 40°C under a 3 bar pressure for 48 hours with palladium on activated carbon (1.3g) as a catalyst. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. Hydrogenation was continued for 24 hours. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/14/1; 20-45 µm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.4g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine; mp. 138°C (interm. 37).

b) Di-tert-butyl dicarbonate (0.02 mol) was added at 5°C to a mixture of intermediate (37) (0.0186 mol) in dichloromethane (60ml). The mixture was stirred at room temperature for 3 hours and poured out into H_2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The product was used without

further purification, yielding 5.9g of (±)-1,1-dimethylethyl [1-[[4-[[1-[(1,1-dimethylethoxy)carbonyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]methyl]-2-methylpropyl]carbamate (interm. 38).

Example A16

A mixture of 1-[4-[[1-(8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (0.0222 mol) and benzenemethanamine (0.0666 mol) in methanol (250ml) was hydrogenated at 40°C under a 3 bar pressure for 24 hours with palladium on activated carbon (1.5g) as a catalyst. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_2Cl_2 and CH_3OH and the filtrate was evaporated. Palladium on activated carbon (1.5g) and methanol (250ml) were added again. Hydrogenation was continued at 40°C under a 3 bar pressure for 24 hours. After uptake of hydrogen, the catalyst was filtered through celite, washed with CH_2Cl_2 and the filtrate was evaporated. The residue (22g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1 and 85/15/1; 20-45 µm). Three pure fractions were collected and their solvents were evaporated, yielding 2.6g 1-[4-[[1-(1,2,3,4-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (interm. 40) (fraction 1), 2.9g of fraction 2 and 0.7g of fraction 3. Fraction 2 and 3 were crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.82g (±)-N-[1-[3-methyl-2-[(phenylmethyl)amino]butyl]-4-piperidinyl]-1-(1,2,3,4-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-amine ; mp. 126°C and 0.55g of *N*-(4-piperidinyl)-1-(1,2,3,4-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-amine; mp. 205°C (comp. 48).

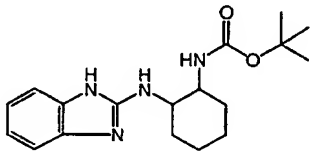
Example A17

a) A mixture of *N*-(4-piperidinyl)-1-(4-quinolinylmethyl)-1*H*-benzimidazol-2-amine (comp. 23) (0.0129 mol), chloroacetonitrile (0.0155 mol), potassium iodide (0.00129 mol) and potassium carbonate (0.0258 mol) in 4-methyl-2-pentanone (80ml) was stirred and refluxed for 5 hours. H_2O was added. The solvent was evaporated. H_2O and CH_2Cl_2 were added. The precipitate was filtered off. The filtrate was separated into its layers. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3.5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.3; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.94g 4-[[1-(4-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidineacetonitrile; mp. 190°C (interm. 41).

b) A mixture of *N*-(4-piperidinyl)-[1,2'-bi-1*H*-benzimidazol]-2-amine (comp. 71) (0.01 mol), chloroacetonitrile (0.01 mol) and sodium hydrogen carbonate (0.02 mol) in

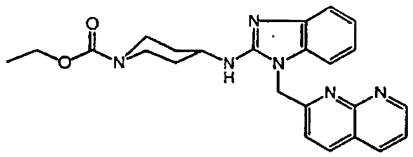
DMF (50ml) was stirred at 50°C overnight. The solvent was evaporated. The residue was taken up in H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was suspended in DIPE, filtered off and dried, yielding 2.3g (63%) of product. This fraction was purified over silica gel on a glass filter (eluent: CH_2Cl_2/(CH_3OH/NH_3) 97/3). The pure fractions were collected and the solvent was evaporated, yielding 1.36g (37%) of 4-[(1,2'-bi-1*H*-benzimidazol-2-yl)amino]-1-piperidine-acetonitrile (interm. 42).

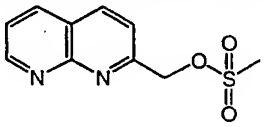
Example A18

Preparation of intermediate  (84)

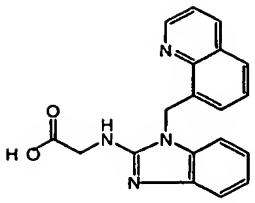
A mixture of 2-chloro-1*H*-benzimidazole (0.0189 mol) and 1,1-dimethylethyl 2-aminocyclohexanecarbamoate (0.04725 mol) (prepared according to A1a))was stirred at 140°C for 3 hours, then brought to room temperature and taken up in CH_2Cl_2/CH_3OH. The same procedure was repeated 3 times on the same quantities of 2-chloro-1*H*-benzimidazole and 1,1-dimethylethyl 2-aminocyclohexanecarbamoate. The mother layers were brought together, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (28g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/ NH_4OH 96/4/0.1; 15-35µm). Two fractions were collected and the solvent was evaporated, yielding 4.5g of intermediate (84) (24%).

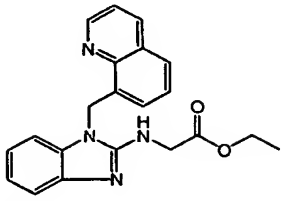
Example A19

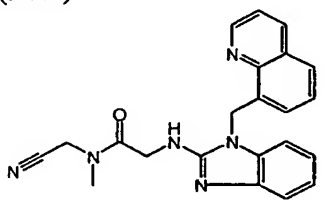
Preparation of intermediate  (76)

A mixture of quantities of ethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidine-carboxylate (0.0154 mol),  (0.0154 mol) (prepared according to A14d) and K_2CO_3 (0.0463 mol) in CH_3CN (50ml) and DMF (5ml) was stirred and refluxed for 6 hours, poured out into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3; 35-70µm). The pure fractions were collected and the solvent was evaporated, yielding: 0.87g of intermediate (76) (13%).

Example A20

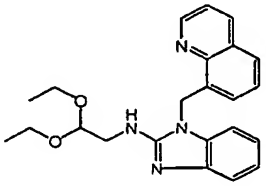
a) Preparation of intermediate  (82)

A solution of  (0.0105 mol) (prepared according to A1b) in HCl 6N (60ml) was stirred and refluxed for 12 hours and then brought to room temperature. The solvent was evaporated. The residue was taken up in 2-propanol. The precipitate was filtered off, washed with CH_3CN, washed with diethyl ether and dried, yielding: 4g of intermediate (82) (94%).

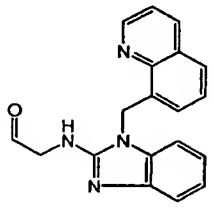
b) Preparation of intermediate  (83)

Intermediate (82 (0.0094 mol) was added at room temperature to CH_2Cl_2 (70ml). Et_3N (0.0188 mol) was added. 1,1'-carbonylbis-1*H*-imidazole (0.0188 mol) was added. The mixture was stirred at room temperature for 4.5 hours. (Methylamino)acetonitrile .HCl (0.0188 mol) was added. The mixture was stirred at room temperature for 12 hours. The organic layer was separated, washed twice with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5; 35-70 µm). The pure fractions were collected and the solvent was evaporated. The residue (2.2g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 1.5g of intermediate (83) (41%).

Example A21

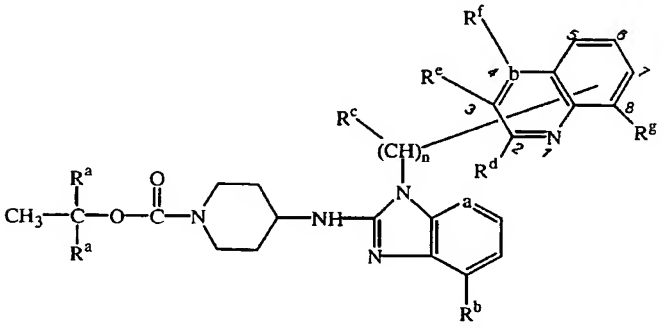
A mixture of intermediate  (interm. 85) (0.0461 mol)

(prepared according to A1b) in HCl 3 N (200ml) was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was taken up in EtOAc and NH4OH. The mixture was stirred for 30 minutes and filtered. The solvent was evaporated. The product was used

without further purification, yielding 14g of  (interm. 86) (100%)

Tables 1, 2 and 3 list intermediates which were prepared analogous to one of the above examples.

Table 1

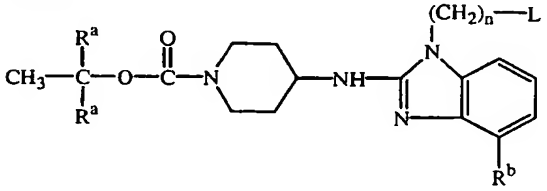


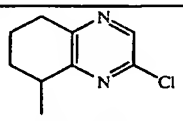
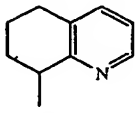
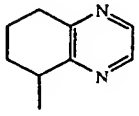
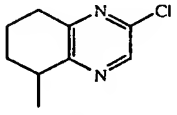
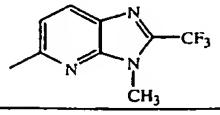
Int. No.	Ex. No.	R^a	R^b	R^c	n	a	*	b	R^d	R^e	R^f	R^g
43	A10c	H	H	H	1	N	2	C	-	H	H	H
44	A12	CH_3	H	$O(CH_2)_2OC_2H_5$	1	CH	8	C	H	H	H	-
45	A12	CH_3	H	$O(CH_2)_2OC_2H_5$	1	CH	2	C	-	H	H	H
46	A7c	CH_3	H	H	1	CH	2	N	-	OCH_3	-	H
47	A7c	H	H	H	1	CH	2	C	-	H	H	Cl
48	A7c	H	H	H	1	CH	2	C	-	H	Cl	H
49	A7c	H	H	H	1	CH	2	C	-	H	H	H
2	A1b	CH_3	H	H	1	CH	2	C	-	H	H	H
50	A12	CH_3	CH_3	OC_2H_5	1	CH	8	C	H	H	H	-
51	A12	CH_3	H	OC_2H_5	1	CH	2	C	-	H	H	H
52	A12	CH_3	H	OC_2H_5	1	CH	2	C	-	OCH_3	H	H
31	A12	CH_3	H	OC_2H_5	1	CH	8	C	H	H	H	-
53	A3f	H	H	H	1	CH	8	C	H	H	H	-
54	A3f	CH_3	H	H	1	CH	8	N	H	H	-	

Int. No.	Ex. No.	R^a	R^b	R^c	n	a	*	b	R^d	R^e	R^f	R^g
55	A7c	CH_3	H	H	1	CH	8	C	CH_3	H	H	-
11	A3f	CH_3	H	H	1	CH	8	N	CH_3	CH_3	-	-
56	A7c	H	H	H	1	CH	4	C	H	H	-	H
57	A7c	H	CH_3	H	1	CH	8	C	H	H	H	-
27	A10c	H	H	H	1	N	8	C	H	H	H	-
58	A10c	H	H	-	0	CH	8	C	H	H	H	-
66	A12	CH_3	CH_3	$O(C_2H_5)OC_2H_5$	1	CH	8	C	H	H	H	-
67	A12	CH_3	H	$O(C_2H_5)OC_2H_5$	1	CH	8	C	H	H	H	-
68	A1b	CH_3	CH_3	CH_3	1	CH	8	C	H	H	H	-
69	A1b	CH_3	H	H	1	CH	2	C	-	OCH_3	H	H
70	A1b	CH_3	H	H	1	CH	2	N	-	H	-	H
71	A1b	CH_3	H	H	1	CH	8	C	OCH_3	H	H	-

* = position bicyclic heterocycle

Table 2



Int. No.	Ex. No.	R^a	R^b	n	L
59	A2c	CH_3	H	0	
60	A8	H	H	0	
61	A2c	H	H	0	
5	A2c	CH_3	H	0	
21	A7c	H	H	1	

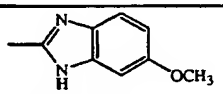
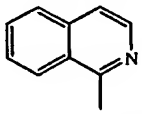
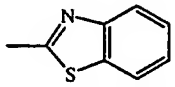
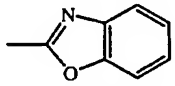
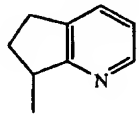
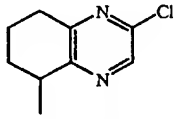
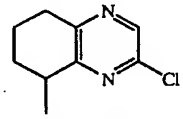
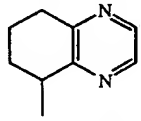
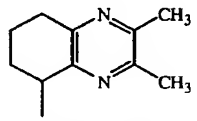
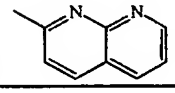
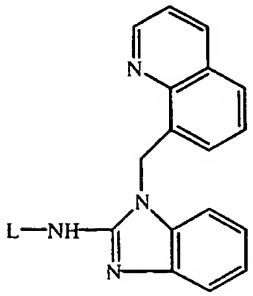
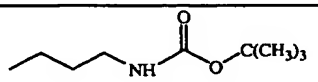
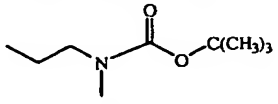
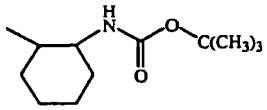
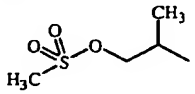
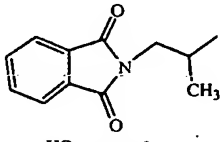
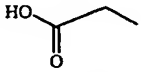
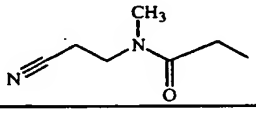
Int. No.	Ex. No.	R^a	R^b	n	L
62	A3f	CH_3	H	1	
63	A7c	CH_3	H	1	
64	A7c	H	H	1	
65	A2c	CH_3	H	0	
22	A8	H	H	0	
72	A2c	CH_3	CH_3	0	
73	A2c	CH_3	CH_3	0	
74	A2c	CH_3	CH_3	0	
75	A2c	CH_3	CH_3	0	
76	A19	H	H	1	

Table 3



Int. No.	Ex. No.	L	Physical data
77	A1b		
78	A1b		
79	A1b		trans
80	A14d		
81	A14e		
82	A20		
83	A20		

B. Preparation of the final compounds

Example B1

a) A mixture of 2-propanol and hydrochloric acid (15ml) was added to a mixture of intermediate (2) (0.0284 mol) in 2-propanol (150ml). The mixture was stirred and refluxed for 90 minutes and cooled. The precipitate was filtered off, washed with 2-propanol and DIPE and dried, yielding 10.36g of *N*-(4-piperidinyl)-1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-amine dihydrochloride (comp.1).

b) A mixture of compound (1) (0.01 mol) and sodium carbonate (0.03 mol) in 4-methyl-2-pentanone (250ml) was stirred and refluxed for a few hours using a water separator (until gas development stops). 2-Bromoethyl carbamic acid 1,1-dimethylethyl ester (0.015 mol) was added. The mixture was stirred and refluxed for 18 hours using a water separator, then cooled, washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/C_2H_5OH 95/5 and 90/10). The pure fractions were collected and the solvent was evaporated, yielding 3.8g of 1,1-dimethylethyl [2-[4-[[1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (comp. 2).

c) A mixture of compound (2) (0.0076 mol) in a mixture of 2-propanol and hydrochloric acid (10ml) and 2-propanol (100ml) was stirred and refluxed for 1 hour

and then cooled. The precipitate was filtered off, washed with 2-propanol and DIPE and dried, yielding 3.08g of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-quinolinylmethyl)-1H-benzimidazol-2-amine tetrahydrochloride monohydrate (comp. 3).

d) A mixture of compound (115) (0.00305 mol) in HBr/HOAc 33% (34ml) was stirred at room temperature for 2 hours, poured out on ice, basified with a concentrated NH_4OH solution and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.2; 15-40 µm). Two fractions (F1 and F2) were collected and their solvents were evaporated, yielding 0.56g F1 (46%) and 0.69g F2 (50%). F1 was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.27g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-amine (comp. 116).

e) A mixture of compound (155) (0.0024 mol) in CH_3OH (3ml) and 2-propanol (15ml) was stirred and refluxed for 2 hours, filtered, washed with 2-propanol and dried. The residue (1.05g) was taken up in CH_2Cl_2 and basified with NH_4OH. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.42g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (0.35g) was dissolved in CH_3OH and converted into the ethanedioic acid salt. The precipitate was filtered off and dried. This fraction was taken up in water and CH_2Cl_2 and alkalized with K_2CO_3 10%. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.21g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 75/28/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.13g of compound (156).

Example B2

A mixture of intermediate (27) (0.02 mol) in hydrochloric acid (6N) (85ml) was stirred and refluxed at 50°C overnight and then brought to room temperature. The solvent was evaporated. The residue was taken up in K_2CO_3 10% and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 5g (69%) of *N*-(4-piperidinyl)-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine (comp. 41).

Example B3

A mixture of intermediate (41) (0.00668 mol) in a solution of ammonia in methanol (7N) (70ml) was hydrogenated at room temperature under a 3 bar pressure for 5 hours

with Raney nickel (2.7g) as a catalyst. After uptake of hydrogen (2 equiv.), the catalyst was filtered through celite, washed with CH_2Cl_2 and CH_3OH and the filtrate was evaporated. The residue was taken up in CH_2Cl_2 and a small amount of CH_3OH. The organic solution was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off and dried, yielding 1.6g (60%) of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-quinolinylmethyl)-1*H*-benzimidazol-2-amine ; mp. 196°C (comp. 24).

Example B4

A mixture of intermediate (36) (0.00351 mol) in hydrazine (2.5ml) and ethanol (30ml) was stirred and refluxed for 20 minutes and brought to room temperature. Ice water was added. The mixture was extracted with CH_2Cl_2 and separated into its layers. The aqueous layer was washed twice with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in diethyl ether. The precipitate was filtered off and dried, yielding 1g of (±)-*N*-[1-[1-(aminomethyl)-2-methylpropyl]-4-piperidinyl]-1-[ethoxy(8-quinolinyl)methyl]-1*H*-benzimidazol-2-amine; mp. 202°C (comp. 100).

Example B5

Intermediate (32) (0.1382 mol) was added at 55°C to a mixture of (±)-1-[ethoxy(3-methoxy-2-quinolinyl)methyl]-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine (0.0346 mol) and potassium carbonate (0.242 mol) in acetonitrile (108ml) and DMF (20ml) (1 equiv of intermediate (32) was added every hour). The mixture was stirred at 55°C for 1 hour and filtered. The filtrate was poured out into H_2O and the mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 98/2/0.4 and 96/4/0.5; 20-45 µm). Two fractions were collected and their solvents were evaporated, yielding 2.5g (23%) of (±)-1,1-dimethylethyl [1-[[4-[[1-[ethoxy(3-methoxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]methyl]-2-methylpropyl]carbamate (comp. 38).

Example B6

A mixture of 1-[4-[[1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-3-methyl-2-butanone (0.0158 mol) and benzenemethanamine (0.0474 mol) in methanol (150ml) was hydrogenated at 40°C under a 3 bar pressure for 48 hours with palladium on activated carbon (0.7g) as a catalyst. After uptake of hydrogen (1 equiv), the catalyst was filtered through celite, washed with CH_2Cl_2/ CH_3OH and the filtrate was evaporated. The residue (11.5g) was purified by column chromatography

over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 94/6/0.5; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 4g of residue. This fraction was converted into the hydrochloric acid salt with 2-propanol/ HCl. The precipitate was filtered off and dried, yielding 5.1g of product. This fraction was converted into the free base and then purified by column chromatography over C_{18} (eluent: CH_3OH/NH_4OAc 60/40 and 80/20; column: KROMASIL C18). Two pure fractions were collected and their solvents were evaporated, yielding 0.8g of fraction 1 and 2g of fraction 2. Fraction 1 was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.5g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-quinolinylmethyl)-1*H*-benzimidazol-2-amine; mp. 135°C (comp. 6). Fraction 2 was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:4). The precipitate was filtered off and dried, yielding 2.2g of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(1,2,3,4-tetrahydro-2-quinolinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydrochloride monohydrate; mp. 230°C (comp. 46).

Example B7

a) A dispersion of sodium hydride in a mineral oil (60%) (0.01 mol) was added portionwise at 0°C under N_2 flow to a mixture of intermediate (38) (0.005 mol) in DMF (25ml). The mixture was stirred at room temperature for 1 hour. A solution of 2-(bromomethyl)-3-methoxyquinoline (0.0055 mol) in DMF (10ml) was added dropwise. The mixture was stirred at room temperature for 2 hours, hydrolized with K_2CO_3 10% and extracted with EtOAc. The organic layer was separated, washed with NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 4.5g (>100%) of (±)-1,1-dimethylethyl [1-[[4-[[1-[(3-methoxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-yl]-amino]-1-piperidinyl]methyl]-2-methylpropyl]carbamate (comp. 14).

b) A dispersion of sodium hydride in a mineral oil (60%) (0.014 mol) was added portionwise at 0°C under N_2 flow to a mixture of intermediate (38) (0.007 mol) in DMF (30ml). The mixture was stirred at 5°C for 1 hour. A solution of (±)-2,8-dibromo-5,6,7,8-tetrahydroquinoline (0.0084 mol) in DMF (10ml) was added dropwise. The mixture was stirred at room temperature for 2 hours. H_2O and EtOAc were added. The organic layer was separated, washed with a saturated NaCl solution, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (5.6g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.5; 20-45 µm). The pure fractions were collected and the solvent was evaporated, yielding 1.1g (25%) of (±)-1,1-dimethylethyl [1-[[4-[[1-(2-bromo-5,6,7,8-tetrahydro-8-quinolinyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]methyl]-2-methylpropyl]-carbamate (comp. 55).

c) A mixture of intermediate 84 (0.0145 mol), 8-bromomethylquinoline (0.0174 mol) and K_2CO_3 (0.029 mol) in CH_3N (70ml) was stirred and refluxed for 4 hours, then brought to room temperature. The solvent was evaporated. The residue was taken up in H_2O and extracted twice with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from diethyl ether/CH_3CN. The precipitate was filtered off and dried, yielding 5.07g of compound 79 (74%).

Example B8

c) (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(5,6,7,8-tetrahydro-3-methoxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydrochloride monohydrate (0.00218 mol) was basified with K_2CO_3 10%. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, to give A'. A mixture of A' in dichloromethane (50ml) was cooled to 0°C. A solution of tribromoborane in dichloromethane (0.01526 mol) was added dropwise. The mixture was stirred at room temperature overnight, poured out on ice, basified with a concentrated NH_4OH solution, decanted and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.1g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/0.5; 20-45 µm). The desired fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:4) with HCl/2-propanol. The precipitate was filtered off and dried, yielding 0.5g (37%) of (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(5,6,7,8-tetrahydro-3-hydroxy-2-quinolinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydro-chloride monohydrate; mp. 240°C (comp. 63).

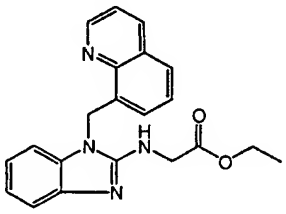
Example B9

a) A mixture of compound 158 (0.0089 mol) in HCl 3N (40ml) was stirred at 100°C for 12 hours, then brought to room temperature and poured out on ice and NH_4OH. EtOAc was added. The precipitate was filtered off, washed with EtOAc and dried, yielding 2g of compound 159.

b) A mixture of compound 168 (0.00895 mol) in HCl 3N (35ml) was stirred at 100°C for 24 hours. The solvent was evaporated. The residue was taken up in EtOAc. The mixture was basified with NH_4OH. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Part of this fraction (0.7g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.3g of compound 167.

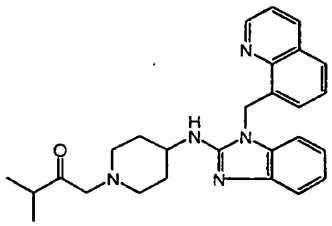
c) A mixture of compound 176 (0.00373 mol) in HCl 3N (20ml) was stirred at 100°C for 12 hours, brought to room temperature, poured out on ice, basified with NH_4OH and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. This fraction was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:3). The precipitate was filtered off and dried, yielding 1.5g of compound 173 (77%).

Example B10

A mixture of intermediate  (interm. 87) (0.002 mol)

(prepared according to A1b)), 1,2-ethanediamine (0.02 mol) and NaCN (0.0002 mol) in CH_3OH (7ml) was heated at 45°C for 4 hours and then brought to room temperature. Water was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.65g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/1; 35-70 µm). The pure fractions were collected and the solvent was evaporated, yielding 0.42g of compound 170 (56%)

Example B11

A mixture of intermediate  (interm. 88) (0.0077 mol)

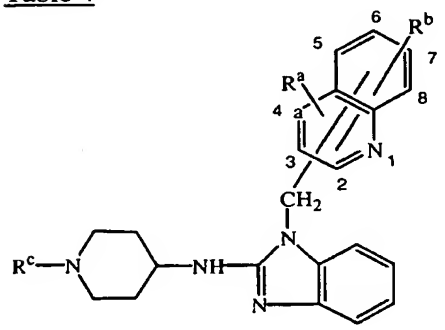
(prepared according to A14a)) and formic acid/NH_3 (0.0462 mol) in formamide (35ml) was stirred at 140°C for 30 min and then brought to room temperature. CH_2Cl_2 was added. The organic layer was separated, washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (4g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1; 15-40 µm). Two pure fractions were collected and their solvents were evaporated. The second fraction was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried, yielding: 1.37g of compound 137 (46%).

Example B12

Isopropyl titanate (IV) (0.0294 mol) was added at room temperature to a mixture of intermediate 85 (0.0245 mol) and 1-acetylpiperazine (0.027 mol) in CH_2Cl_2 (50ml) and ethanol (50ml). The mixture was stirred at room temperature for 7 hours. $NaBH_3CN$ (0.0245 mol) was added portionwise. The mixture was stirred at room temperature for 12 hours. H_2O was added. The mixture was filtered over celite and washed with CH_2Cl_2. The filtrate was separated into its layers. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (6.7g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.2; 15-40 µm). The pure fractions were collected and the solvent was evaporated. This fraction was crystallized from 2-propanone. The precipitate was filtered off and dried, yielding: 0.64g of compound 176.

Tables 4 to 13 list the compounds of formula (I) which were prepared according to one of the above examples.

Table 4

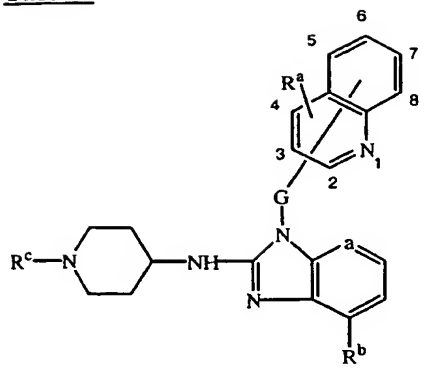


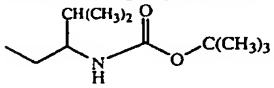
Comp No.	Ex. No.	a	R^a	R^b	*	R^C	Physical data
1	B1a	CH	H	H	2	H	HCl (1:2)
2	B1b	CH	H	H	2	**	
3	B1c	CH	H	H	2	$CH_2CH_2NH_2$	HCl(1:4);H_2O(1:1)
4	B1a	CH	H	H	8	H	
5	B1a	CH	H	H	2	H	
6	B5	CH	H	H	2	CH_2CH(2-propyl)NH_2	
7	B3	CH	H	H	8	CH(2-propyl)CH_2NH_2	
8	B3	CH	H	H	2	CH(2-propyl)CH_2NH_2	H_2O (1:1)
9	B1a	CH	H	8-Cl	2	H	HCl (1:2)
10	B1c	CH	H	H	8	CH_2CH(2-propyl)NH_2	
11	B3	CH	H	8-Cl	2	CH(2-propyl)CH_2NH_2	
12	B1a	CH	4-OH	H	2	H	

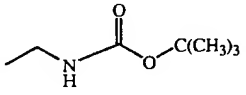
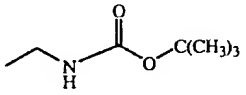
Comp No.	Ex. No.	a	R^a	R^b	*	R^C	Physical data
13	B3	CH	H	8-Cl	2	$CH_2CH(2\text{-propyl})NH_2$	
14	B6a	CH	3-OCH_3	H	2	$(C=O)OC(CH_3)_3$	
15	Blc	CH	3-OCH_3	H	2	$CH_2CH(2\text{-propyl})NH_2$	
16	B6a	N	3-CH_3	H	2	***	
17	Bla	CH	H	H	8	H	HCl (1:3)
18	Bla	N	H	H	8	H	
19	Blc	N	H	H	8	$CH_2CH(2\text{-propyl})NH_2$	HCl(1:3); H_20(1:3)
20	Bla	N	3-OCH_3	H	2	H	
21	B4	N	3-OCH_3	H	2	***	
22	Blc	N	3-OCH_3	H	2	$CH_2CH(2\text{-propyl})NH_2$	
23	Bla	CH	H	H	4	H	
24	B2	CH	H	H	4	$CH_2CH_2NH_2$	
88	Bla	N	2-CH_3	3-CH_3	8	H	
89	Blc	N	2-CH_3	3-CH_3	8	$CH_2CH(2\text{-propyl})NH_2$	HCl(1:4);H_2O(1:2)
90	Bla	CH	2-CH_3	H	8	H	
91	B1c	CH	2-CH_3	H	8	$CH_2CH(2\text{-propyl})NH_2$	H_2O (1:1)
92	B2	CH	2-CH_3	H	8	$CH_2CH_2NH_2$	
104	B3	CH	H	H	8	$CH_2CH(2\text{-propyl})NH_2$	
105	B3	CH	H	H	8	$CH(2\text{-propyl})CH_2NH_2$	
106	B1c	N	3-CH_3	H	2	$CH_2CH(2\text{-propyl})NH_2$	H_20 (1:2)
109	B5	CH	H	H	8	***	
110	B5	N	2-CH_3	3-CH_3	8	***	
111	B5	CH	2-CH_3	H	8	***	
112	B5	N	H	H	8	***	
113	B7	CH	H	H	8	***	

- * position bicyclic heterocycle
- ** $(CH_2)_2NH(C=O)OC(CH_3)_3$
- *** $CH_2CH(2\text{-propyl})NH(C=O)OC(CH_3)_3$

Table 5



Comp No.	Ex. No.	a	R^a	R^b	*	R^c	G	Physical data
25	B1a	CH	H	H	2	H	$CHOC_2H_5$	
26	B3	CH	H	H	2	CH(2-propyl)CH_2NH_2	$CHOC_2H_5$	H_2O (1:1)
27	B3	CH	H	H	2	CH_2CH(2-propyl)NH_2	$CHOC_2H_5$	
28	B1a	CH	H	H	2	H	***	
29	B3	CH	H	H	2	CH(2-propyl)CH_2NH_2	***	H_2O (1:1)
30	B1a	CH	H	H	8	H	***	
31	B3	CH	H	H	8	CH_2CH(2-propyl)NH_2	***	
32	B3	CH	H	H	8	CH(2-propyl)CH_2NH_2	***	
33	B1a	CH	H	H	8	H	$CHOC_2H_5$	
34	B1a	CH	3-OCH_3	H	2	H	$CHOC_2H_5$	
35	B1a	N	H	H	2	H	CH_2	
36	B4	N	H	H	2	**	CH_2	
37	B1c	N	H	H	2	CH_2CH(2-propyl)NH_2	CH_2	HCl (1:4)
38	B4	CH	3-OCH_3	H	2	**	$CHOC_2H_5$	
39[9]	B1c	CH	3-OCH_3	H	2	CH_2CH(2-propyl)NH_2	$CHOC_2H_5$	HCl (1:3); H_2O (1:2)
40	B2	N	H	H	2	$CH_2CH_2NH_2$	CH_2	
41	B1a	N	H	H	8	H	CH_2	
42	B1c	N	H	H	8	CH_2CH(2-propyl)NH_2	CH_2	
43	B1a	CH	H	CH_3	8	H	CH_2	
44	B1a	CH	H	CH_3	8	H	$CHOC_2H_5$	
45	B2	N	H	H	8	$CH_2CH_2NH_2$	CH_2	
100	B3	CH	H	H	8	CH(2-propyl)CH_2NH_2	$CHOC_2H_5$	
107	B1c	CH	H	H	8	CH_2CH(2-propyl)NH_2	$CHOC_2H_5$	
115	B5	CH	H	CH_3	8		CH_2	
116	B1d	CH	H	CH_3	8	CH_2CH(2-propyl)NH_2	CH_2	

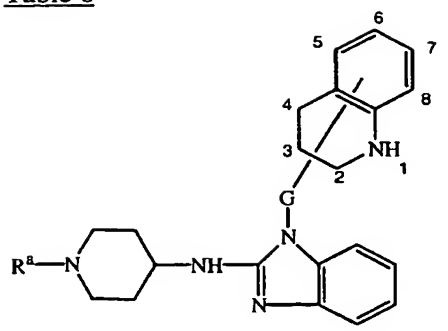
Comp No.	Ex. No.	a	R^a	R^b	*	R^c	G	Physical data
117	B1d	CH	H	CH_3	8	CH=O	CH_2	
118	B1d	CH	H	CH_3	8	$CH_2CH_2NH_2$	***	H_2O(1:1)
119	B1d	CH	H	CH_3	8	CH_2CH(2-propyl)NH_2	***	
120	B3	N	H	CH_3	8	$CH_2CH_2NH_2$	CH_2	HCl(1:4); H_2O(1:3)
121	B1d	CH	H	CH_3	8	CH=O	***	
122	B1c	N	H	CH_3	8	CH_2CH(2-propyl)NH_2	CH_2	HCl(1:4); H_2O(1:1)
123	B1d	CH	H	CH_3	8	$CH_2CH_2NH_2$	CH_2	
124	B1c	CH	H	H	8	$CH_2CH_2NH_2$	***	HCl(1:3); H_2O(1:2)
125	B1c	CH	H	CH_3	8	$CH_2CH_2NH_2$	$CHCH_3$	H_2O(1:1)
126	B1d	CH	3-OCH_3	H	2	$CH_2CH_2NH_2$	CH_2	H_2O(1:2)
127	B1c	CH	4-CH_3	H	2	CH_2CH(2-propyl)NH_2	CH_2	HCl(1:4); H_2O(1:1)
128	B1c	CH	H	H	8	$CH_2CH_2NH_2$	CH_2	HCl(1:4); H_2O(1:1)
129	B1c	CH	H	H	8	$CH_2CH_2NH_2$	$CHCH_3$	H_2O(1:1)
130	B1c	CH	4-CH_3	H	2	$CH_2CH_2NH_2$	CH_2	HCl(1:4); H_2O(1:2)
131	B1c	CH	H	H	4	CH_2CH(2-propyl)NH_2	CH_2	HCl(1:4); H_2O(1:2)
131	B1b	CH	H	CH_3	8		CH_2	
132	B1b	CH	H	H	8		CH_2	
133	B2	CH	H	H	8	H	$CHCH_3$	HCl(1:2); H_2O(1:2)
134	B1c	CH	H	H	2	$CH_2CH_2NH_2$	$CHCH_3$	H_2O(1:1)
135	B2	CH	4-CH_3	H	2	H	CH_2	HCl(1:2)
136	B2	N	H	CH_3	8	H	CH_2	
137	B11	CH	H	H	8	CH=O	CH_2	

* position quinoline

** CH_2CH(2-propyl)$NH(C=O)OC(CH_3)_3$

*** $CHO(CH_2)_2OC_2H_5$

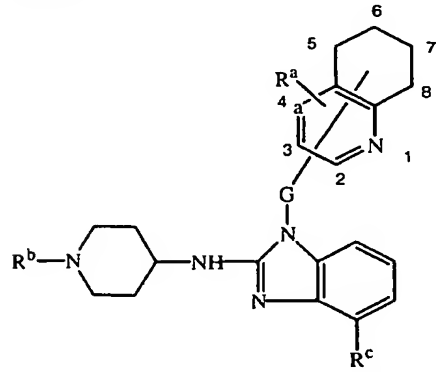
Table 6



Comp. No.	Ex. No.	*	G	R^a	Physical data
46	B5	2	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
47	B5	8	CH_2	CH_2CH(2-propyl)NH_2	HCl(1:4);H_2O(1:1)
48	B5	8	-	H	
49	B5	8	-	CH_2CH(2-propyl)NH_2	H_2O (1:1)

* position bicyclic heterocycle

Table 7

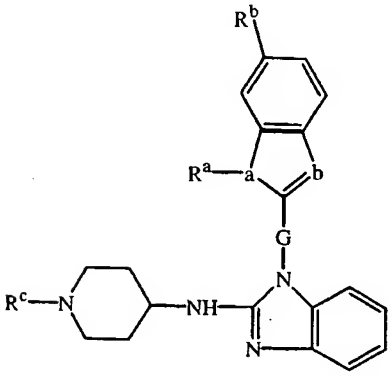


Co. No.	Ex. No.	*	a	R^a	G	R^b	R^c	Physical data
50	B1a	8	CH	H	-	H	H	
51	B5	8	CH	H	-	CH_2CH(2-propyl)NH_2	H	
52	B1a	8	N	H	-	H	H	HCl (1:3)
53	B3	8	N	H	-	CH(2-propyl)CH_2NH_2	H	
54[3]	B3	8	N	H	-	CH_2CH(2-propyl)NH_2	H	H_2O (1:1)
55	B6b	8	CH	2-Br	-	**	H	
56	B1c	8	CH	2-Br	-	CH_2CH(2-propyl)NH_2	H	HCl(1:3);H_2O(1:3)
57	B6b	8	CH	2-CH_3	-	**	H	

Co. No.	Ex. No.	*	a	R^a	G	R^b	R^c	Physical data
58	B1c	8	CH	2-CH_3	-	CH_2CH(2-propyl)NH_2	H	HCl(1:4);H_2O(1:1)
59	B6a	2	CH	H	CH_2	**	H	
60	B1c	2	CH	H	CH_2	CH_2CH(2-propyl)NH_2	H	HCl(1:4);H_2O(1:1)
61	B6a	2	CH	3-OCH	CH_2	**	H	
62	B1c	2	CH	3-OCH	CH_2	CH_2CH(2-propyl)NH_2	H	HCl(1:4);H_2O(1:1)
63	B7	2	CH	3-OH	CH_2	CH_2CH(2-propyl)NH_2	H	HCl(1:4);H_2O(1:1)
64	B1a	8	N	3-Cl	-	H	H	
65	B4	8	N	3-Cl	-	**	H	
66	B1c	8	N	3-Cl	-	CH_2CH(2-propyl)NH_2	H	HCl(1:3);H_2O(1:1)
67	B2	8	N	H	-	$CH_2CH_2NH_2$	H	HCl(1:3);H_2O(1:3)
68	B1a	8	N	2-Cl	-	H	H	
69	B4	8	N	2-Cl	-	**	H	
70[10]	B1c	8	N	2-Cl	-	CH_2CH(2-propyl)NH_2	H	HCl(1:3);H_2O(1:1)
139	B1c	5	N	3-Cl	-	$CH_2CH_2NH_2$	CH_3	HCl(1:3);H_2O(1:2)
140	B1d	5	N	H	-	CH_2CH(2-propyl)NH_2	CH_3	
141	B1c	5	N	2-Cl	-	$CH_2CH_2NH_2$	CH_3	HCl(1:3);H_2O(1:3)
142	B1c	5	N	2-Cl	-	CH_2CH(2-propyl)NH_2	CH_3	

- * position bicyclic heterocycle
- ** CH_2CH(2-propyl)$NH(C{=}O)OC(CH_3)_3$

Table 8

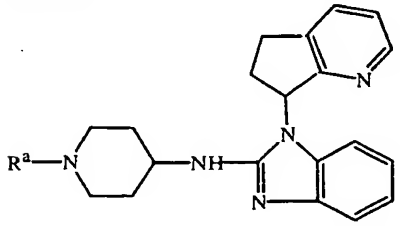


Comp. No	Ex. No.	a	b	R^a	R^b	G	R^c	Physical data
71		N	N	H	H	-	H	
72		S	N	-	H	-	H	HBr(1:2);H_2O(2:1)
73	B1a	O	N	-	H	-	H	

Comp. No	Ex. No.	a	b	R^a	R^b	G	R^c	Physical data
74		N	N	H	H	CH_2	H	
75		N	N	H	H	CH_2	$CH_2CH_2NH_2$	H_2O (1:1)
76		O	CH	-	H	CH_2	H	
77		N	N	CH_3	H	CH_2	H	
78	B1c	N	N	CH_3	H	CH_2	$CH_2CH_2NH_2$	
79		S	CH	-	H	CH_2	H	
80	B1a	S	N	-	H	CH_2	H	HCl(1:2);H_2O(1:1)
81	B2	N	N	H	H	-	$CH_2CH_2NH_2$	HCl(1:4)
82	B1a	N	N	H	OCH_3	CH_2	H	
83	B1b	S	N	-	H	-	*	H_2O (1:1)
84	B1c	S	N	-	H	-	$CH_2CH_2NH_2$	HCl(1:3);H_2O(1:1)
85	B1b	N	N	CH_3	H	CH_2	*	
86	B1b	O	N	-	H	-	*	
87	B1c	O	N	-	H	-	$CH_2CH_2NH_2$	

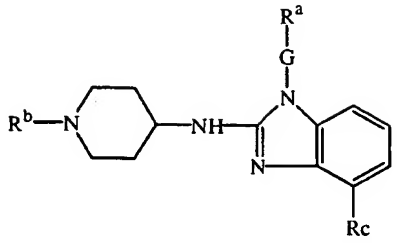
* $CH_2CH_2NH(C=O)OC(CH_3)_3$

Table 9

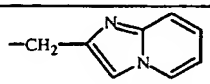
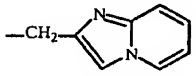
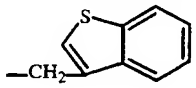
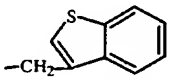
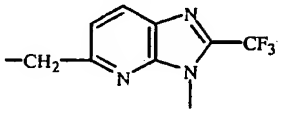
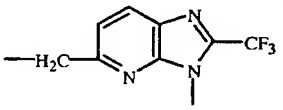
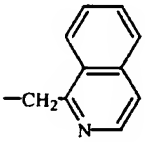
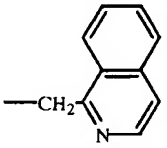
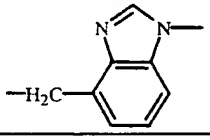


Comp. No.	Ex. No.	R^a	Physical data
102	B1a	H	HCl (1:3)
103	B5	CH_2CH(2-propyl)NH_2	H_2O (1:1)

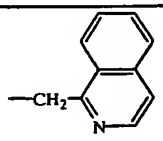
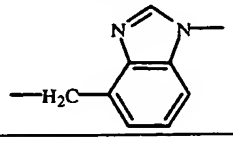
Table 10



Rnr

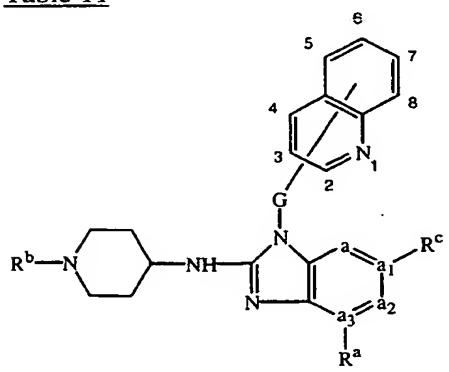
Comp. No.	Ex. No.	R^b	R^c	G-R^a	Physical data
93		H	H		
101		$CH_2CH_2NH_2$	H		
94		$CH_2CH_2NH(C=O)OCH_2CH_3$	H		
95		$CH_2CH_2NH_2$	H		
96	B1a	H	H		
97	B2	$CH_2CH_2NH_2$	H		HCl(1:3);H_2O(1:1)
98	B1a	H	H		
99	B1c	CH_2CH(2-propyl)NH_2	H		HCl(1:3);H_2O(1:3)
108	B5	CH_2CH(2-propyl)NH_2	H		

Rnr

Comp. No.	Ex. No.	R^b	R^c	G-R^a	Physical data
114		*	H		
143	B6	CH_2CH(2-propyl)NH_2	CH_3		

* CH_2CH(2-propyl)$NH(C{=}O)OC(CH_3)_3$

Table 11

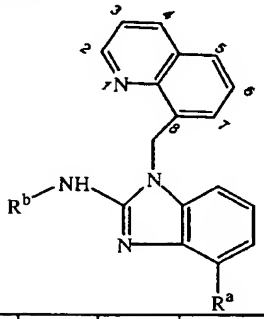


Co No.	Ex. No.	a-a1-a2-a3	*	R^a	R^c	R^b	G	Physical data
144	B1c	CH=N-CH=C	8	H	-	CH_2CH(2-propyl)NH_2	CH_2	HCl(1:3); H_2O(1:4)
145	B1c	CH=C-N=C	8	H	H	CH_2CH(2-propyl)NH_2	CH_2	HCl(1:3); H_2O(1:2)
146	B1c	CH=C-C=N	8	-	H	CH_2CH(2-propyl)NH_2	CH_2	HCl(1:3); H_2O(1:2)
147	B2	CH=C-CH=C	8	CH_3	Cl	H	CH_2	
148	B3	CH=N-CH=C	8	H	-	$CH_2CH_2NH_2$	$CHOC_2H_5$	
149	B2	CH=C-CH=N	8	-	H	H	CH_2	HCl(1:2); H_2O(1:1)
150	B1c	CH=C-CH=C	7	CH_3	Cl	$CH_2CH_2NH_2$	CH_2	HCl(1:4); H_2O(1:2)
151	B3	CH=N-CH=C	8	H	-	$CH_2CH_2NH_2$	CH_2	

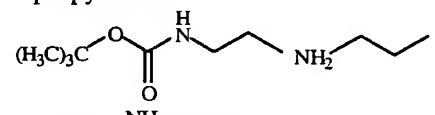
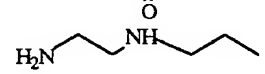
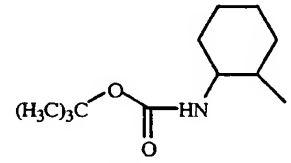
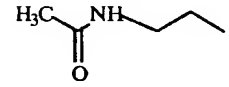
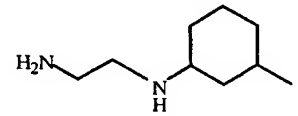
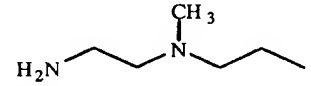
Co No.	Ex. No.	a-a1-a2-a3	*	R^a	R^c	R^b	G	Physical data
152	B2	CH=N-CH=C	8	H	-	H	CH_2	HCl(1:4); H_2O(1:2)
153	B3	CH=C-CH=N	8	-	H	$CH_2CH_2NH_2$	$CHOC_2H_5$	

o position bicyclic heterocycle

Table 12



o

Co No.	Ex. No.	R^a	R^b	Physical data
154	B1c	H	3-propylamine	HCl(1:3);H_2O(1:1)
155	B1b	H		
156	B1e	H		
157	B7c	H		trans
158	B7c	H		
159	B9a	H	2-ethylamine	
160	B1c	H	3-propylmethylamine	
161	B1c	H		cis;HCl(1:3);H_2O(1:1)
162	B1c	H		HCl(1:4);H_2O(1:1)
163	B4	H	3-isobutylamine	
164	B1c	H	2-ethylmethylamine	HCl(1:2)

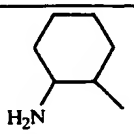
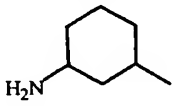
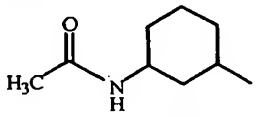
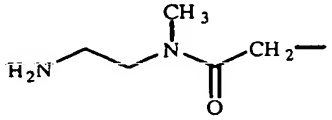
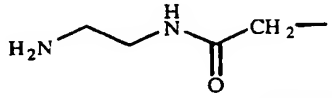
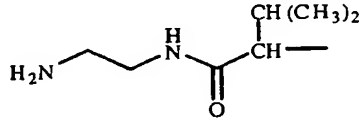
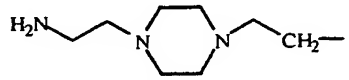
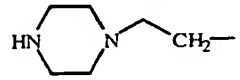
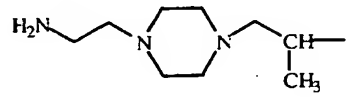
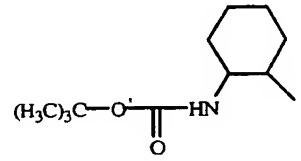
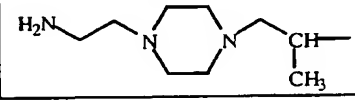
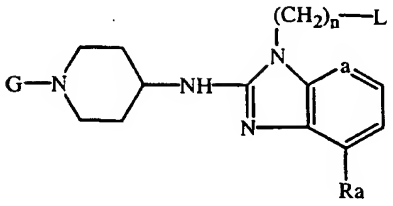
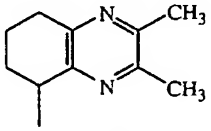
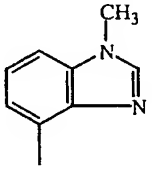
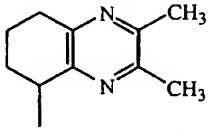
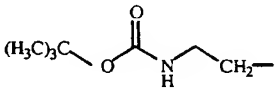
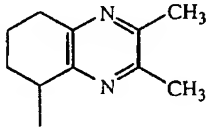
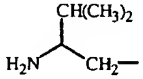
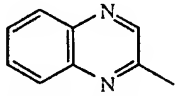
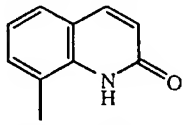
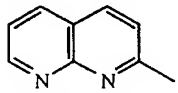
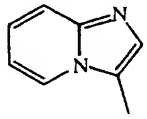
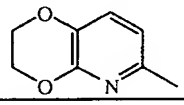
Co No.	Ex. No.	R^a	R^b	Physical data
165	B1a	H		trans;H_2O(1:1)
166	B9a	CH_3	2-ethylamine	
167	B9b	H		cis
168	B7c	H		cis
169	B3	H		HCl(1:3);H_2O(1:2)
170	B10	H		
171	B10	H		H_2O(1:1)
172	B1c	H		HCl(1:4);H_2O(1:2)
173	B9c	H		HCl(1:3)H_2O(1:2)
174	B1c	H		
175	B7c	H		cis
176	B12	H		

Table 13



Co No.	Ex. No.	G	L	a.	R_a.	Physical data
177	B1d	2-ethylamine		CH	H	HCl(1:3);H_2O (1:3)
178	B1c	2-ethylamine		N	H	HCl(1:4);H_2O (1:4)
179	B1c	2-ethylamine		CH	CH3	H_2O(1:1)
180	B1b			CH	H	
181	B1c			CH	H	HCl(1:3);H_2O (1:2)
182	B1c	2-ethylamine		CH	H	HCl(1:3);H_2O (1:2)
183	B1c	2-ethylamine		CH	H	
184	B1c	2-ethylamine		CH	H	HCl(1:4);H_2O (1:1)
185	B1d	2-ethylamine		CH	H	$C_2H_2O_4$(2:7)

5

Table 14: Physical data

Comp. No.	C		H		N		melting point
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	
1	61.40	60.70	5.85	6.04	16.27	15.54	
3	51.08	51.16	6.07	6.35	14.89	14.17	
4	73.92	73.29	6.49	6.52	19.59	19.38	206°C
6	73.27	73.12	7.74	7.73	18.99	18.77	135°C
7	73.27	71.85	7.74	7.80	18.99	18.61	188°C
8	70.40	69.73	7.88	7.40	18.24	17.56	80°C
9							> 250°C
10	73.27	72.82	7.74	7.58	18.99	18.63	172°C
11							190°C
13	67.98	66.43	6.97	6.79	17.62	17.02	164°C
15	71.16	70.66	7.68	7.58	17.78	17.81	210°C
19	51.45	51.64	6.97	6.89	16.15	15.96	240°C
22	68.47	68.04	7.45	7.52	20.70	20.55	206°C
23	73.92	71.70	6.49	6.53	19.59	19.92	140°C
24	71.97	69.89	7.05	7.10	20.98	20.07	196°C
89	51.46	53.22	6.94	7.11	15.00	15.14	24°C
91	70.85	69.82	8.07	8.29	17.71	17.48	180°C
92	72.43	71.51	7.29	7.30	20.27	20.10	176°C
104	72.87	70.26	7.53	7.27	19.61	18.73	88°C
105	72.87	71.37	7.53	7.39	19.61	19.39	135°C
106	65.69	66.19	7.96	7.62	19.86	19.71	110°C
26	69.02	69.16	7.99	7.68	16.65	16.79	140°C
27	71.57	70.60	7.87	7.80	17.27	17.14	166°C
29	67.86	67.64	8.08	7.79	15.32	15.15	100°C
31	70.16	68.97	7.98	7.97	15.84	15.56	110°C
32	70.16	69.35	7.98	8.34	15.84	14.73	98°C
33	71.79	70.72	6.78	7.17	17.44	16.69	145°C
37							215°C
39							209°C
40	68.80	66.01	6.78	6.60	24.42	23.31	138°C
42	70.40	69.14	7.50	7.50	22.10	21.68	180°C
43	74.36	73.02	6.78	6.65	18.85	18.41	155°C
44	72.26	71.53	7.03	7.26	16.85	16.40	186°C
45	68.80	66.74	6.78	6.64	24.42	23.77	178°C
100	71.57	71.16	7.87	7.93	17.27	17.44	202°C
107	71.57	69.77	7.87	7.85	17.27	16.40	78°C

Comp. No.	C		H		N		melting point
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	
46							230°C
47							230°C
48	72.59	71.54	7.25	7.13	20.16	19.91	205°C
49	69.30	70.08	8.50	8.37	18.65	18.93	140°C
51	72.19	70.66	8.39	8.43	19.43	18.79	120°C
53	69.25	68.88	8.14	8.28	22.61	22.23	
54	66.49	66.30	8.26	7.77	21.71	21.53	144°C
56	46.27	47.19	6.57	6.44	12.45	12.16	> 250°C
58							210°C
60							212°C
62	52.51	53.38	7.24	7.63	13.12	12.37	240°C
63	51.76	52.74	7.08	7.32	13.41	12.93	240°C
66	50.43	50.60	6.60	6.58	16.47	16.28	> 250°C
67	47.62	46.73	6.90	6.83	17.67	17.19	230°C
70							238°C
80							210°C
81	48.38	47.77	5.61	5.61			
82	67.00	66.51	6.43	6.29	22.32	22.12	
83	61.15	62.11	6.71	6.60	16.46	16.88	
84	48.51	48.46	5.62	5.35	16.16	16.03	
87	67.00	66.42	6.43	6.55	22.32	21.80	
103	68.78	68.77	8.31	8.23	19.25	18.78	88°C
96	58.73	58.59	5.16	5.03	22.83	22.40	144°C
97							210°C
99	53.51	52.63	7.15	7.02	13.87	13.24	200°C
108	70.08	68.99	7.92	8.10	22.00	21.65	160°C
116							203°C
117							218°C
141							225°C
177							>260°C
139							190°C
118							48°C
144							220°C
143	70.55	66.03	8.11	8.14	21.33	18.98	
119							145°C
121							185°C
140							172°C
120							210°C

Comp. No.	C		H		N		melting point
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	
142							98°C
122							245°C
154							90°C
145							190°C
123							194°C
124							150°C
146							240°C
125							74°C
178							160°C
150							>250°C
126							90°C
127							200°C
128							210°C
157							185°C
159							140°C
151							212°C
160	73.02	72.95	6.71	6.70	20.27	20.35	
129							170°C
130							150°C
131							>250°C
152							230°C
153							169°C
131							120°C
161							206°C
132							160°C
133							210°C
134							81°C
162							210°C
147							>250°C
163							168°C
179							116°C
135	62.16	62.10	6.12	6.06	15.76	15.71	
164							146°C
136							188°C
165							112°C
166							114°C
149							210°C
180							247°C

Comp. No.	C		H		N		melting point
	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	
167							167°C
181							235°C
182							>250°C
184	47.75	47.58	6.01	6.37	17.72	17.00	
169							180°C
170							73°C
171							72°C
172							178°C
173							190°C
137							196°C
175							228°C
176							168°C
185							158°C

C. Pharmacological example

Example C1 : In vitro screening for activity against Respiratory Syncytial Virus.

The percent protection against cytopathology caused by viruses (antiviral activity or IC_{50}) achieved by tested compounds and their cytotoxicity (CC_{50}) were both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC_{50} (cytotoxic dose for 50% of the cells) by the IC_{50} (antiviral activity for 50 % of the cells).

Automated tetrazolium-based colorimetric assays were used for determination of IC_{50} and CC_{50} of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 $TCID_{50}$ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row to measure the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4×10^5 cells/ml) of HeLa cells was added to all wells in a volume of 50µl. The cultures were incubated at

37°C in a 5% CO_2 atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

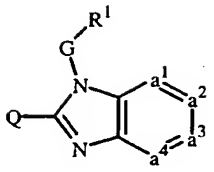
Particular IC_{50}, CC_{50} and SI values are listed in Table 15 hereinbelow.

Table 15

Co. No.	IC_{50} (µM)	CC_{50} (µM)	SI
42	0.0004	>10.05	>25119
31	0.0008	12.68	15849
56	0.0016	12.71	7943
145	0.00631	25.12	3981
6	0.0126	10.00	794
156	0.01259	19.95	1585
131	0.0316	19.94	631
53	0.1259	>9.95	>79
29	0.3162	10.12	32
148	1	25	25
97	1.5849	>99.85	>63

Claims

1. A compound of formula



(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

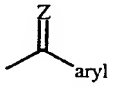
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

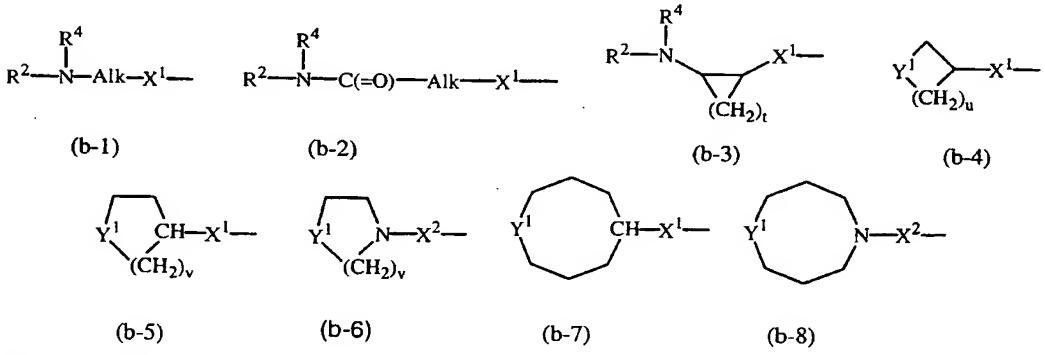
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula



wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula



(b-1) (b-2) (b-3) (b-4) (b-5) (b-6) (b-7) (b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

t is 2, 3, 4 or 5;

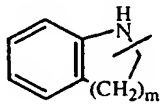
u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

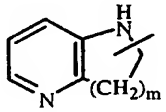
whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl optionally substituted with one, two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, arylcarbonyl, HO(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, amino, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino and aryl;

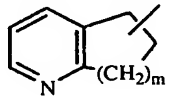
R^1 is a bicyclic heterocycle selected from quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-b]pyridinyl, 3*H*-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-b]pyridyl or a radical of formula



(c-1)



(c-2)



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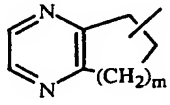
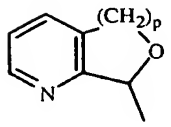
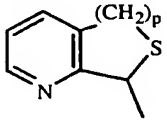


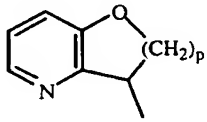
(c-4)



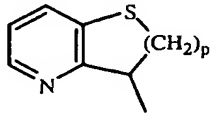
(c-5)



(c-6)



(c-7)



(c-8)

and said bicyclic heterocycles may optionally be substituted in either of the two cycles with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxy-C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)-amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

each m independently is 1 or 2;

each p independently is 1 or 2;
each R^2 independently is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;
R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;
R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;
R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;
aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;
Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

2. A compound according to claim 1 wherein $-a^1=a^2-a^3=a^4-$ is a radical of formula (a-1), (a-2) or (a-3).

3. A compound according to claim 1 or 2 wherein Q is a radical of formula (b-5) wherein v is 2 and Y^1 is $-NR^2-$.

4. A compound according to anyone of claims 1 to 3 wherein R^2 is C_{1-10}alkyl substituted with NHR^6.

5. A compound according to anyone of claims 1 to 4 wherein G is a direct bond or C_{1-10}alkanediyl optionally substituted with one, two or three substituents selected from hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$.

6. A compound according to claim 1 wherein the compound is selected from (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-4-methyl-1-[1-(8-quinolinyl)ethyl]-*1H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-bromo-5,6,7,8-tetrahydro-8-quinolinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-4-methyl-*1H*-benzimidazol-

2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(1-methyl-*1H*-benzimidazol-4-yl)methyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(ethoxy-8-quinolinylmethyl)-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-7-methyl-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine tetrahydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-7-methyl-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine tetrahydrochloride monohydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(8-quinolinylmethyl)-*1H*-imidazo[4,5-c]pyridin-2-amine trihydrochloride dihydrate; *N*-[1-(2-aminoethyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-amine; *N*-[1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-yl]-1,3-propanediamine trihydrochloride monohydrate; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-*1H*-benzimidazol-2-amine trihydrochloride dihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(8-quinolinylmethyl)-*1H*-imidazo[4,5-b]pyridine-2-amine trihydrochloride dihydrate; (±)-*N*-[1-[1-(aminomethyl)-2-methylpropyl]-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-3-(2-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine trihydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(1-isoquinolinylmethyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-(quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-(8-quinolinylmethyl)-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine trihydrochloride.trihydrate; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(5,6,7,8-tetrahydro-2,3-dimethyl-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl-1-(3-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-1-(3-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine trihydrochloride dihydrate; (±)-*N*-[1-(2-

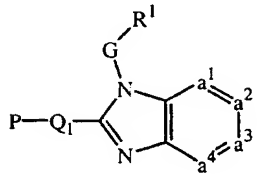
aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)-8-quinolinylmethyl]-4-methyl-*1H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-c]pyridin-2-amine trihydrochloride tetrahydrate; (±)-*N*-[1-(2-aminoethyl)-4-piperidinyl]-3-(8-quinolinylmethyl)-3*H*-imidazo[4,5-b]pyridin-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(1-methyl-*1H*-benzimidazol-4-yl)methyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-(2-chloro-5,6,7,8-tetrahydro-5-quinoxalinyl)-4-methyl-*1H*-benzimidazol-2-amine; a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof.

7. A compound according to any one of claims 1 to 6 for use as a medicine.

8. A pharmaceutical compositioncomprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 6.

9. A process of preparing a composition as claimed in claim 8, characterized in that, a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as described in any one of claims 1 to 6.

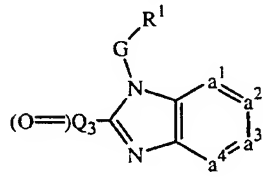
10. An intermediate of formula



(IV)

with R^1, G and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, P being a protective group, and Q_1 being defined as Q according to claim 1 but being devoided of the R^2 or R^6 substituent.

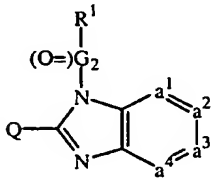
11. An intermediate of formula



(IX)

with R^1, G and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(O=)Q_3$ being a carbonyl derivative of Q, said Q being defined according to claim 1, provided that it is devoided of the NR^2R^4 or NR^2 substituent.

12. An intermediate of formula

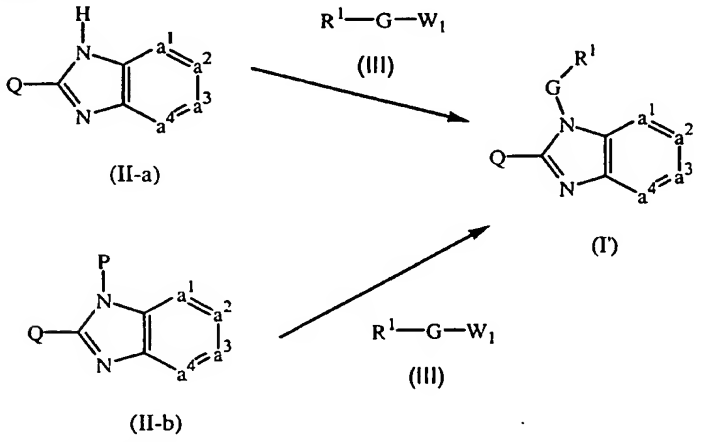


(XXII)

with R^1, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(O=)G_2$ being a carbonyl derivative of G, said G being defined according to claim 1.

13. A process of preparing a compound as claimed in claim 1, characterized by,

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)

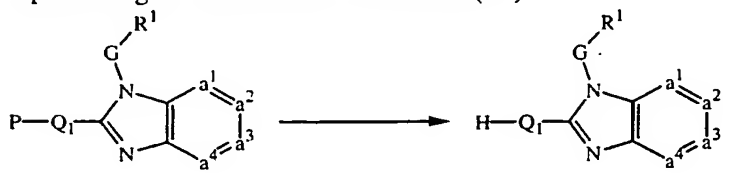


(II-a) (III) (I')

(II-b) (III)

with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

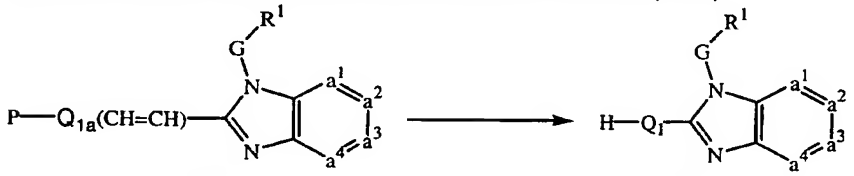
b) deprotecting an intermediate of formula (IV)



(IV) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

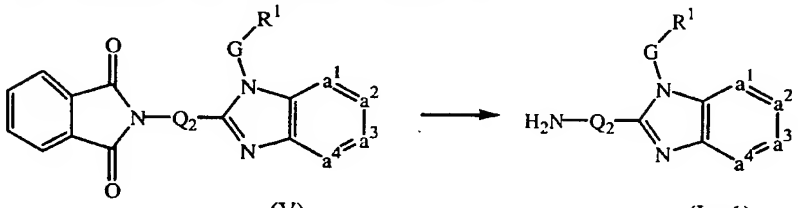
c) deprotecting and reducing an intermediate of formula (IV-a)



(IV-a) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, Q_{1a}(CH=CH) being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group;

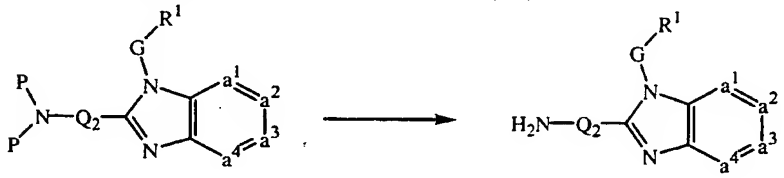
d) deprotecting an intermediate of formula (V)



(V) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

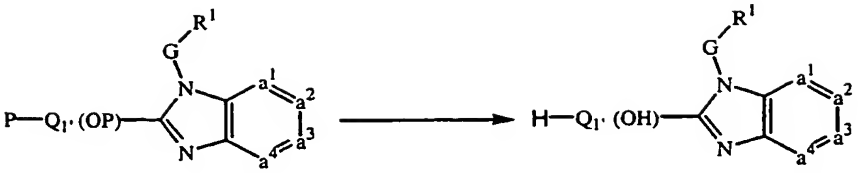
e) deprotecting an intermediate of formula (VI)



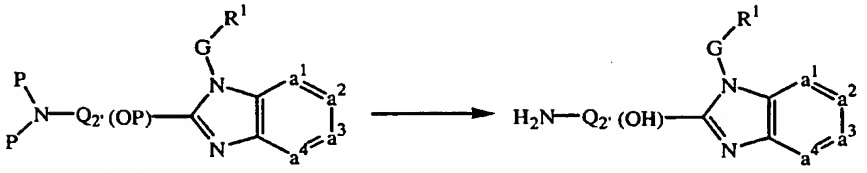
(VI) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

f) deprotecting an intermediate of formula (VII) or (VIII)



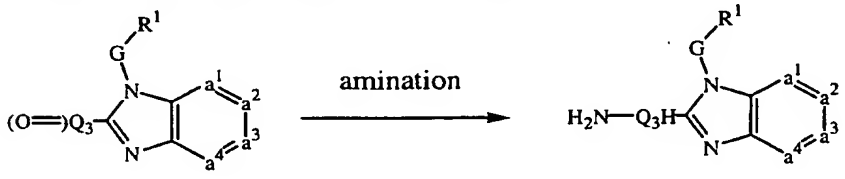
(VII) (I-a-2)



(VIII) (I-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H-Q_1\cdot(OH)$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, $H_2N-Q_2\cdot(OH)$ being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

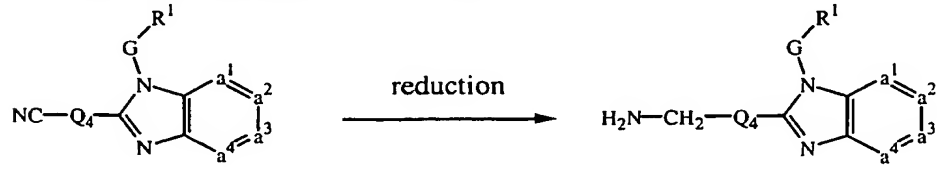
g) amination of an intermediate of formula (IX)



(IX) (I-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_3H being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

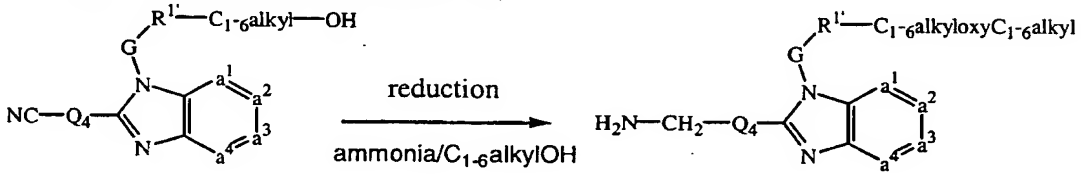
h) reducing an intermediate of formula (X)



(X) (I-a-1-3)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

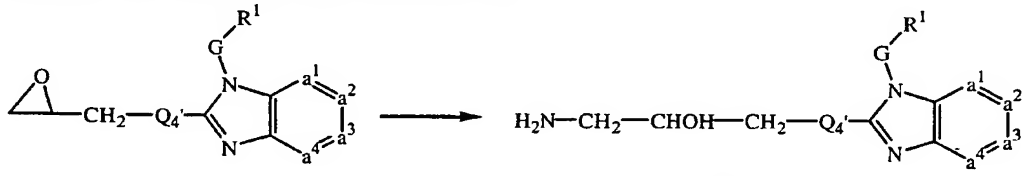
i) reducing an intermediate of formula (X-a)



(X-a) (I-a-1-3-1)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, and $R^{1'}$ being defined as R^1 according to claim 1 provided that it comprises at least one substituent, in the presence of a suitable reducing agent and suitable solvent;

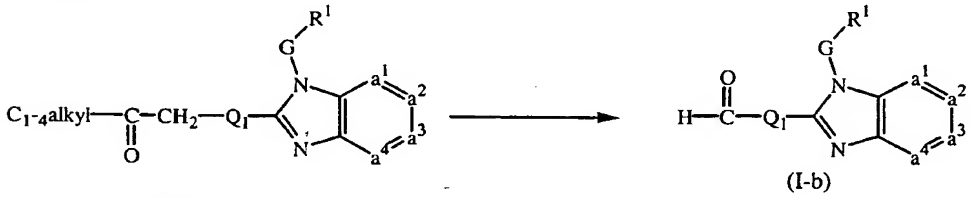
j) amination of an intermediate of formula (XI)



(XI) (I-a-1-3-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-CHOH-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of a suitable amination reagent;

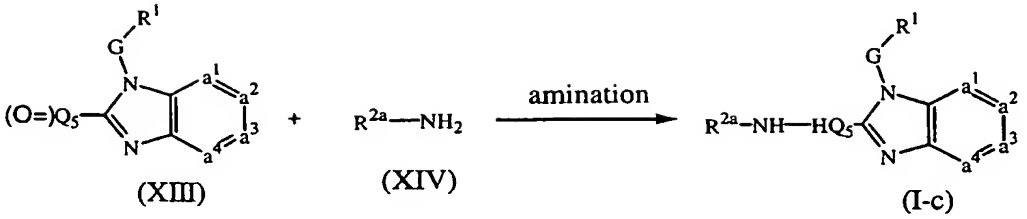
k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



(XII) (I-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H-C(=O)-Q_1$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is formyl;

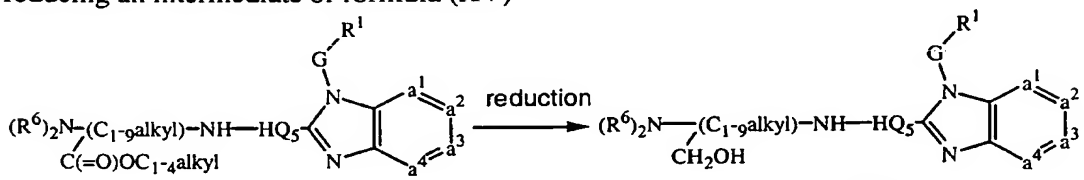
l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)



(XIII) (XIV) (I-c)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and R^{2a}-NH-HQ_5 being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent;

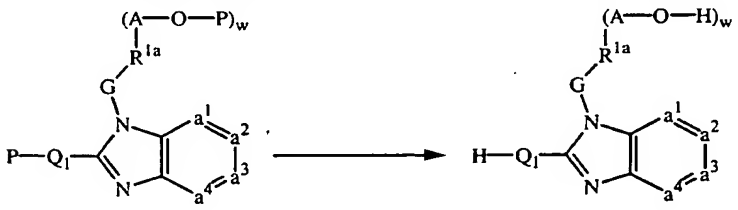
m) reducing an intermediate of formula (XV)



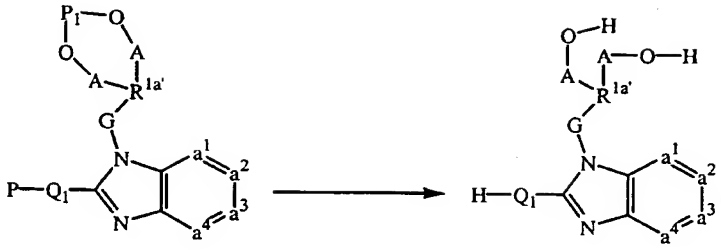
(XV) (I-c-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(R^6)_2N$-[$(C_{1-9}$alkyl$)CH_2OH$]-NH-HQ_5 being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by C_{1-10}alkyl substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a suitable reducing agent;

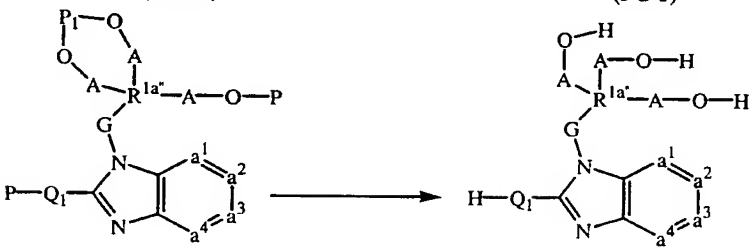
n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)



(XVI) (I-d)



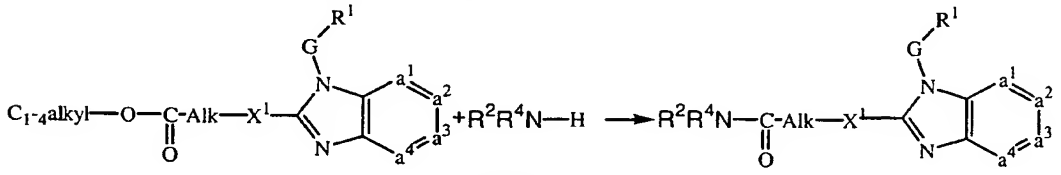
(XVI-a) (I-d-1)



(XVI-b) (I-d-2)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H-Q_1$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and R^{1a}-(A-O-H)$_w$, $R^{1a'}$-(A-O-H)$_2$ and $R^{1a''}$-(A-O-H)$_3$ being defined as R^1 according to claim 1 provided that R^1 is substituted with hydroxy, hydroxyC_{1-6}alkyl, or $HO(-CH_2-CH_2-O)_n-$, with w being an integer from 1 to 4 and P or P_1 being a suitable protecting group, with a suitable acid.

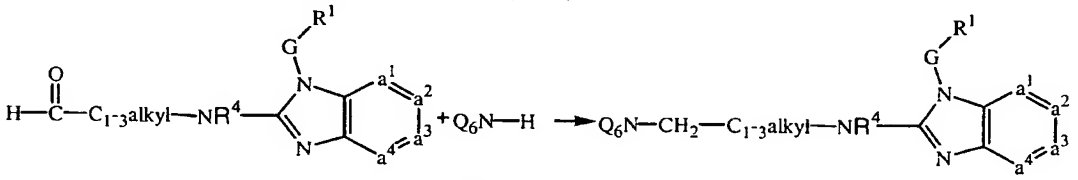
o) amination of an intermediate of formula (XVII)



(XVII) (XVIII) (I-e)

with R^1, G, $-a^1=a^2-a^3=a^4-$; Alk, X^1 R^2 and R^4 defined as in claim 1, in the presence of a suitable amination agent;

p) amination of an intermediate of formula (XIX)

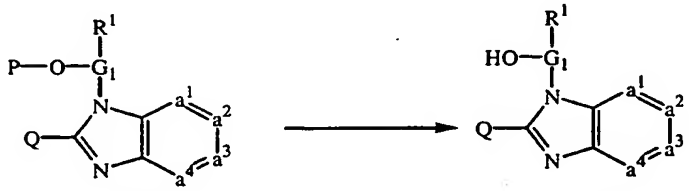


(XIX) (XX) (I-p)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $Q_6N-CH_2-C_{1-3}$alkyl-NR^4

being defined as Q according to claim 1 provided that in the definition of Q, X^2 is C_{2-4}alkyl-NR^4, in the presence of a suitable amination agent;

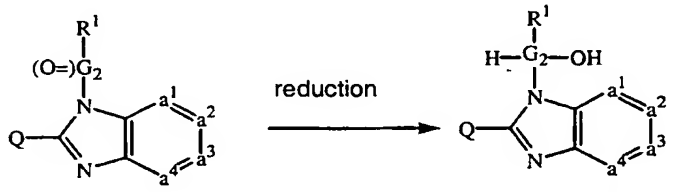
q) deprotecting an intermediate of formula (XXI)



(XXI) (I-q)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and HO-G_1 being defined as G according to claim 1 provided that G is substituted with hydroxy or HO-$(CH_2CH_2O-)_n$;

r) reducing an intermediate of formula (XXII)



(XXII) (I-q-1)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H-G_2-OH being defined as G according to claim 1 provided that G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, in the presence of a suitable reducing agent.

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, metal complexes, quaternary amines or *N*-oxide forms thereof.

14. A product containing (a) a compound as defined in claim 1, and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in the treatment or the prevention of viral infections.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound as defined in claim 1, and (b) another antiviral compound.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 00/05677

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 A61K31/4709 A61K31/4375 A61K31/437 A61K31/498
A61K31/4409 A61K31/436 A61P11/00 A61P31/12 C07D471/04
C07D417/14 C07D413/14 C07D409/14 C07D401/06 C07D491/056

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 01697 A (JANSSEN PHARMACEUTICA NV) 6 February 1992 (1992-02-06) page 21, line 9 - line 12; claim 1	1,7
P,X	WO 99 44596 A (JANSSEN PHARMACEUTICA) 10 September 1999 (1999-09-10) page 11, line 18 - line 19; claim 1	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	27/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 00/05677

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 //(C07D471/04,221:00,221:00),(C07D471/04,235:00,221:00), (C07D491/056,319:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna' al Application No
PCT/EP 00/05677

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9201697 A	06-02-1992	AT	188477 T	15-01-2000
		AU	646280 B	17-02-1994
		AU	8209391 A	18-02-1992
		CA	2086546 A	20-01-1992
		CN	1058216 A,B	29-01-1992
		CS	9102239 A	19-02-1992
		DE	69131895 D	10-02-2000
		DE	69131895 T	20-07-2000
		EP	0539420 A	05-05-1993
		ES	2142802 T	01-05-2000
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		GR	3032999 T	31-07-2000
		HU	64066 A	29-11-1993
		IL	98865 A	27-11-1995
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		MX	9100307 A	28-02-1992
		NO	304791 B	15-02-1999
		NZ	238863 A	26-03-1993
		PL	170580 B	31-01-1997
		PT	98366 A,B	29-05-1992
		RU	2067978 C	20-10-1996
		US	5360807 A	01-11-1994
		ZA	9105654 A	31-03-1993
WO 9944596 A	10-09-1999	AU	3408999 A	20-09-1999

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 00 05677

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 to 15. relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I where Q is a 1-R2-piperidyl-4-amino or amino(cyclo)alkylamino group and their intermediates as described in the examples of tables 3 to 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Copy for the elected Office (EO/US)

10/019376

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

To:
QUAGHEBEUR, Luc
Janssen Pharmaceutica N.V.
Patent Department - 3547
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

Date of mailing (*day/month/year*) 04 December 2001 (04.12.01)	
Applicant's or agent's file reference JAB 1500-PCT	**REPLY DUE** see paragraph 1 below
International application No. PCT/EP00/05677	International filing date (*day/month/year*) 20 June 2000 (20.06.00)
Applicant JANSSEN PHARMACEUTICA N.V.	

1. ☐ REPLY DUE within _____ months/days from the above date of mailing

☐ NO REPLY DUE, however, see below

☒ IMPORTANT COMMUNICATION

☐ INFORMATION ONLY

2. COMMUNICATION:

It has been brought to the attention of the International Bureau that in respect of the above-identified application, the international publication No. WO 01/00615 published on 04 January 2001 (04.01.01) erroneously indicated the name of one inventor and applicant as ANDRIES, Koenraad Jozef Lodenwijk Marcel. The correct name is ANDRIES, Koenraad Jozef **Lodewijk** Marcel.

The International Bureau shall republish a correction in Section II of the PCT Gazette. A corrected version of the corresponding PCT pamphlet will be published as early as possible.

A copy of this Notification is being sent to the receiving Office (RO/EP) and to the designated/elected Offices concerned.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
Anman QIU

Telephone No. (41-22) 338.83.38

P; ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 February 2001 (02.02.01)	
International application No. PCT/EP00/05677	**Applicant's or agent's file reference** JAB 1500-PCT
International filing date (day/month/year) 20 June 2000 (20.06.00)	**Priority date** (day/month/year) 28 June 1999 (28.06.99)
Applicant JANSSENS, Frans, Eduard et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 November 2000 (18.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38